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Detection of Cancer Predisposition: Laboratory Approaches

Monograph No. 3

Editors:

Lawrence Spatz, PhD

Arthur D. Bloom, MD

Natalie W. Paul



**Environmental
Health Institute**
BERKSHIRE HEALTH SYSTEMS

**March of
Dimes**
Preventing
Birth Defects

DETECTION OF CANCER PREDISPOSITION: LABORATORY APPROACHES

Monograph No. 3

**ENVIRONMENTAL HEALTH INSTITUTE
Pittsfield, Massachusetts**

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PREFACE

As scientific understanding of the process of carcinogenesis has become more detailed and sophisticated, we have learned that cancer is, in most cases, a disease arising from the effect of environmental exposures on specific genes and chromosomes operating in particular genetic constitutions. As described in Monograph No. 2 of this series (*Genetic Susceptibility to Environmental Mutagens and Carcinogens*, A.D. Bloom, L. Spatz, and N.W. Paul, eds., 1989), the genetic components of carcinogenesis, such as the role of oncogenes and antioncogenes in cancer and the nature of the predisposing genetic backgrounds, have been intensively investigated in recent years. As a consequence, many laboratory approaches to the detection of cancer predisposition are now feasible.

Because of its commitment to do critical assessments of important basic environmental health issues, with a particular emphasis on genetic-environmental interactions, the Environmental Health Institute convened a study group to evaluate laboratory approaches to cancer susceptibility. The Fellows of the Institute who participated in this study group were: Drs. Richard Erbe, James German, Frank Gonzalez, Theodore Krontiris, Thomas Roderick, Mark Rothstein, Jack Taylor, and Wendell Weber. The editors are grateful to this superb group of scientists for their insights during our discussions over the past year and for the excellence of their contributed pieces.

The study itself was funded by an award to EHI from the National Institute of Environmental Health Sciences, NIH, U.S. Public Health Service, under contract number NO1-ES-75185. Drs. David Hoel and Michael Hogan of NIEHS served as project officers and Mr. Phillip Jones has continued to serve ably as contract officer.

We thank the March of Dimes Birth Defects Foundation, and Ms. Natalie W. Paul and Dr. Beverly Raff in particular, for their continuing active support in the preparation and publication of this Monograph. We also thank those EHI staff members—Ms. Christine Rodick, Ms. Debra Deres, Ms. Laura Hansen and Dr. Diane Brenner—who, in various significant ways, assisted the work of the study group and of the editors.

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Pittsfield, Massachusetts
January, 1990

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EXECUTIVE SUMMARY

The existence of a genetic predisposition to cancer has long been inferred from those rare genetic disorders, such as ataxia telangiectasia and Bloom syndrome, in which an increased incidence of several types of cancer is one manifestation of the syndrome. The predisposition has also been inferred from the rare familial forms of particular cancers, such as retinoblastoma (RB). Although the analyses of these conditions have provided significant insights into mechanisms of carcinogenesis, the contribution of these conditions to the overall incidence of human cancer is small, on the order of a few percent, because of their relative infrequency. As understanding of the mechanisms of carcinogenesis has increased, it has become clear that cancer arises through a multistep process in which some of the crucial steps involve alterations of specific genetic targets. The recognition of the importance of genetic alterations in the genesis of cancer and the acquisition of a detailed knowledge of oncogenic changes at specific genetic loci have led to the realization that the genetic predisposition to cancer arises not only from specific alterations of oncogenes and antioncogenes, but also from any of a variety of situations in which either genetic instability and/or the likelihood of genetic damage are increased. The search for cancer predisposition has thus expanded to include, among others, DNA repair defects, chromosomal fragile sites, unique oncogene structures and genetic polymorphisms affecting the ways in which drugs and xenobiotics are metabolized to DNA-reactive intermediates. The effects of many of these are likely to be evident only in conjunction with particular environmental exposures, with cancers most likely to arise in exposed individuals whose genetic constitutions render them most sensitive to carcinogen effects. The epidemiologic significance of cancer predisposition in this broader view may, then, be far greater than inferred from the rare genetic cancer syndromes and may play a very significant role in the genesis of human disease.

This volume summarizes the present state of our knowledge of the methods available for detecting this predisposition to cancer, the difficulties attendant on their application, and the likely directions of future research in this field. From the technical point of view, most of the laboratory techniques described are standard ones available in most biochemical, cytogenetic and molecular biology laboratories. However, at the present time, few of the tests described have been adequately validated in large, prospective population-based studies. Because the interest of the public in cancer predisposition is so high and these tests are so readily performed (and so potentially profitable), the entrepreneurial spirit may lead to premature introduction of inadequately documented

procedures. Furthermore, there are many social and ethical problems attendant upon the introduction of even well-proven tests of genetic predisposition, and some of these problems are considered here.

In the first two chapters, Gonzalez and Weber describe the known genetic polymorphisms of drug and xenobiotic metabolism that have been identified, and present the evidence linking them to cancer predisposition. Chapter 3, by Yunis, is devoted to a consideration of chromosomal fragile sites as specific loci at which genetic alterations are likely to occur and that may, therefore, be implicated in carcinogenesis. In Chapter 4, German summarizes the cytogenetic effects of DNA-repair deficiency diseases and how these relate to the increased cancer incidence seen in these conditions. Taylor, in Chapter 5, reviews the epidemiologic evidence for genetic susceptibility to cancer and considers methodologic problems involved in collecting these data. In Chapter 6, Krontiris discusses the significance and origin of rare oncogene restriction fragment length polymorphisms (RFLPs) which have an increased incidence in cancer patients. Chapter 7, by Roderick, approaches cancer predisposition via a comparative model in which known predisposing genes in rodents may be putatively located and searched for in humans. The final chapter, by Rothstein, reviews some of the ethical and legal issues that are likely to arise out of the availability and use of screening tests for cancer predisposition.

CHAPTER SUMMARIES

Chapter 1 (F. Gonzalez) and Chapter 2 (W. Weber)

Virtually all organisms have evolved enzymatic mechanisms to detoxify potentially harmful foreign substances (xenobiotics). In mammals, this is usually accomplished in two phases: an initial oxygenation by one of a host of membrane-bound cytochrome P450 enzymes, followed by enzymatic conjugation with sulfate or glucuronide and excretion in urine. The regulation and expression of these detoxifying enzymes is under genetic control and polymorphisms occur frequently. It is widely acknowledged that many carcinogens require metabolic activation to forms that react with DNA in order to exert their effects. Paradoxically, in many cases the enzymes responsible for activating carcinogens are the very ones that are supposed to detoxify them: the cytochromes P450, in the course of oxygenating some compounds, generate reactive intermediates that can react with DNA. Protection from these P450-generated reactive species is afforded through another group of enzymes, the phase II enzymes, such as glutathione transferases and epoxide hydrolases, some of which are also genetically polymorphic. Because of the complex interactions among the various enzyme systems, it will be most useful to consider the overall pattern and complement of enzymes in determining an individual's susceptibility to carcinogens. We recognize, too, that any predis-

position arising by these mechanisms presumably requires exposure to a carcinogen to manifest itself.

The cytochromes P450 comprise a superfamily of related enzymes with as many as 50 members. They are presumed to have arisen originally when animals emerged from an aquatic environment and began to feed on terrestrial plants that contained toxins. A unique battery of P450s was evolved by each species to inactivate the toxins in the plants on which it fed. P450 expression and activities thus tend to be species-specific and variable, changing through natural selection with changing toxin exposures. The P450s are also characterized by very broad substrate specificities and slow turnover numbers; many are inducible. At least two of the cytochrome P450s have been implicated in cancer predisposition: P450 IID1 (debrisoquine hydroxylase) and P450 IA1 (aryl hydrocarbon hydroxylase).

About 10% of Europeans cannot make a functional P450 IID1 enzyme and about three-quarters of these individuals have been shown to make an abnormally short mRNA transcript from the IID1 gene that codes for an unstable and inactive enzyme. The risk of lung cancer among smokers is clustered among individuals having the highest levels of enzyme activity. A similar association may exist for bladder cancer.

Cytochrome P450 IA1 is an inducible enzyme that is not expressed in the absence of polycyclic aromatic hydrocarbon inducers. Considerable interindividual variability in inducibility has been observed. Several studies have shown that bronchogenic carcinoma in smokers is associated with high inducibility of this enzyme.

Various techniques have been used in the phenotyping of individuals for these polymorphisms. Administration of doses of debrisoquine and collection of urine for assay of parent compound and the 4-OH derivative formed by P450 IID1 can distinguish extensive metabolizers (EM) from poor metabolizers (PM). DNA probes can detect up to 70% of PM, using RFLP analysis of lymphocyte DNA; further research may permit the development of methods for the identification of the remaining 30% of PMs and for distinguishing homozygous from heterozygous EMs. The inducibility of P450 IA1 has been assessed in lymphocytes in cultures incubated in the presence and absence of inducing aromatic hydrocarbons.

Another genetically polymorphic enzyme of drug metabolism that appears to be significant for cancer predisposition is N-acetyl transferase (NAT). Originally recognized more than 30 years ago during investigations of differences in response of subjects to the anti-tuberculosis drug, isoniazid, NAT is now known to be an enzyme capable not only of metabolizing drugs but also of participating in the activation of arylamine carcinogens to forms that can bind to DNA as mutagenic adducts. Synthesis of the enzyme, a monomeric protein of MW-32kD, is specified by a single autosomal locus at which rapid and slow

alleles have been identified. Human populations are thus trimodally distributed among homozygous slow acetylators and heterozygous and homozygous rapid acetylators.

The association between acetylator phenotype and cancer predisposition is complex, varying with tissue tumor type. Bladder cancers among workers exposed to arylamines, such as benzidine, are strongly associated with the slow acetylator phenotype. Colon cancers, on the other hand, appear to be more prevalent among rapid acetylators. In some preliminary studies, breast cancer appears to be associated with rapid acetylator status, whereas laryngeal and gastric cancers are more common in slow acetylators. The fact that both slow and rapid acetylation are associated with cancers in different tissues relates to the complexities of the process by which arylamine carcinogens are activated: NAT does not act on its own but does so in conjunction with other enzymes whose activities may vary from tissue to tissue, with carcinogens being activated in both acetylated and nonacetylated forms.

Techniques for acetylator phenotyping have been extensively investigated. At the present time, the most satisfactory method employs test doses of caffeine and analysis of the appropriate metabolites in urine. It is possible in this way to obtain genotypes, as a trimodal distribution is observed in which the expected numbers of homo- and heterozygotes are present. Cloning of the human NAT gene is close to being achieved and may lead to the availability of gene probes that will allow genotyping to be performed on lymphocyte DNA.

It is possible that other genetic polymorphisms, related to other members of the extensive P450 gene family or to other genes involved in carcinogen activation or inactivation, may exist and may contribute to cancer risk. For example, polymorphism of the phase II enzyme, trans-stilbene oxide glutathione transferase has recently been suggested as a marker for susceptibility to lung cancer: among smokers, lung cancers cluster in those individuals with low levels of enzyme activity. The complex patterns of xenobiotic metabolism that are the result of an interacting network of enzymes are to a great extent under genetic control and may prove to be crucial determinants of susceptibility to carcinogens.

Chapter 3 (Yunis)

Fragile sites are specific locations at which chromosomes, under a wide variety of conditions, are most likely to develop breaks or gaps. Originally described as rare, inherited chromosomal variants (designated h-fra) that were present infrequently in the general population, it was subsequently found that many fragile sites could be induced when cells were cultured in thymidine deficient media (c-fra). Homologous fragile sites were also observed in chimpanzee and gorilla chromosomes. As cytogenetic analysis of cancers became more sophisticated, it was appreciated that many of the c-fra and

h-fra sites were at the same chromosomal loci as the loci of the rearrangements and deletions that were characteristic of cancer cells. Subsequently, many mutagens and carcinogens were shown to induce fragile sites in chromosomes, with many of these coinciding with cancer breakpoints. In addition, many of these same sites are the location at which sister chromatid exchanges and meiotic recombination occur. Experiments in which DNA-cleaving enzymes are introduced into cells have shown that similar constellations of fragile sites can be generated in this manner as well. These observations, taken together, suggest that there are specific, sensitive sites in chromatin at which the DNA is "exposed" and at which breaks that may lead to malignancy can occur. It is not presently known whether these sites share common DNA sequences that are hypersensitive or whether these sites reflect a particular chromatin structure that renders the DNA more accessible, as might be expected for transcriptionally active genes. Analysis of fragile sites at the molecular level is now being undertaken and should provide the necessary information to resolve the issue. Since fragile sites have been found repeatedly to be among the loci at which rearrangements and deletions occur in cancer cells, it is reasonable to suppose that structural changes at fragile sites in particular individuals, that render those individuals more susceptible to breakage, might predispose to cancer. Although some observations lend support to this concept, further studies, particularly at the molecular level, are clearly needed.

Chapter 4 (J. German)

The chromosome-breakage syndromes, a group of rare, recessively transmitted genetic diseases characterized by increased instability of DNA in somatic cells, all appear to include some degree of cancer predisposition among their symptoms. For some of these conditions, there is reasonably good evidence that the observed instability is due to defects in the cellular mechanisms that repair DNA damage; in others, the nature of the biochemical defects is unknown. Included among these syndromes are xeroderma pigmentosum (XP), Bloom syndrome (BS), Fanconi anemia (FA), ataxia telangiectasia (AT) Werner syndrome (WS) and the Nijmegen breakage syndrome (NBS). Each of these is an independently inherited clinical entity; in addition, four of the six appear to have multiple complementation groups (XP, FA, AT, NBS), each of which presumably represents a defect at a discrete genetic locus. Thus, in the aggregate, these diseases delineate at least 19 different genetic loci which, when defective, result in chromosomal instability and cancer predisposition. Although the number of genes is large and the cancer predisposition often quite marked, these conditions, because they are rare and recessively inherited, do not account for the majority of human neoplasia. At present, it is not possible to say whether heterozygote carriers of these genes have any

increase in cancer predisposition. In theory, if heterozygote effects do exist, then these genes might play a major role in causing cancer in human populations, because, although homozygotes are rare, phenotypically normal individuals carrying at least one of the many mutations, would be relatively common. An increased risk of breast cancer in obligate heterozygote carriers of the AT gene has been reported in one study; on the other hand, no increase in somatic mutations was observed in heterozygous carriers of either AT or BS.

Each chromosome-breakage syndrome is characterized by a distinctive clinical phenotype and a particular pattern of cytogenetic abnormalities. In BS, AT, FA and NBS, PHA-stimulated but otherwise untreated lymphocyte cultures display distinct cytogenetic anomalies; in WS, abnormalities are evident in untreated skin fibroblast cultures. The defect in XP cells is not readily apparent in untreated cells, but is clearly manifest after exposure to ultraviolet light. Cells from all of the syndromes (with the possible exception of WS, which may not have been examined) manifest abnormal responses to a variety of DNA-damaging agents such as radiation, ethylmethanesulfonate, diepoxybutane, and mitomycin C. Thus, most of these diseases (AT, FA, BS, NBS) are associated with cytogenetic abnormality and instability both in the presence and absence of known mutagens. Four of the six syndromes (FA, BS, XP, WS) can be distinguished by the distinctive patterns of their cytogenetic anomalies alone, while NBS and AT show the same pattern of cytogenetic instability and radiosensitivity, but have distinct phenotypes clinically.

These rare syndromes are of considerable importance in delineating the multiple pathways by which genetic predisposition to cancer can arise. A great deal of research effort is currently focused on defining, locating and characterizing the defective genes in these disorders. It is hoped that identification of candidate genes and characterization of the mutants will permit identification of heterozygotes by molecular means so that the question of whether cancer predisposition occurs in heterozygotes may be addressed.

Chapter 5 (J. Taylor)

There is considerable epidemiologic evidence for genetic susceptibility to cancer. Some ethnic differences in cancer incidence are striking. For example, Ewing sarcoma is essentially a disease of whites, with non-whites apparently much less frequently affected. There are also some substantial ethnic variations in age-specific incidences of particular cancers (such as testicular cancer and acute lymphocytic leukemia) and in incidence of cancer at specific subsites (such as gastric cancer of the pyloric antrum) that are thought to reflect the genetic susceptibilities of specific ethnic groups.

Population-based genealogic studies have found an excess of certain single cancers and sets of cancers among closely related persons, as compared to a

computer-simulated genealogy in which cancer cases are assigned randomly. Familial cancer syndromes, though rare, are well recognized and family clusters of cancers at many sites have been described. Family clusters must be interpreted with caution, however, because they may reflect common environmental factors as well.

Cancer studies based on genealogy, family clusters or ethnicity are descriptive in nature and cannot elucidate the underlying biologic mechanisms leading to predisposition. In order to obtain a detailed mechanistic understanding of cancer predisposition it is necessary to combine epidemiologic studies with the techniques of molecular biology and biochemistry that can provide detailed genotypic and phenotypic data concerning specific loci. These multidisciplinary studies depend on finding the candidate genes, defining their phenotypes or markers that correlate with cancer risk, and then analyzing the genes in detail. This approach has been highly successful of late, as, for example, in the identification of the RB gene, the tumor-suppressor gene deleted in retinoblastoma. The candidate gene was identified through segregation analysis in family studies. Linkage analysis, in which an array of polymorphic marker genes are examined to find associations between specific alleles and cancer risk, is another useful approach. The marker gene that is associated with cancer risk indicates the chromosomal location of the cancer-susceptibility gene that may then be sought out by gene cloning techniques. This approach will become more feasible as more and more marker genes become available. It is expected that epidemiologic studies will become increasingly interdisciplinary, employing techniques of molecular biology, biochemistry and cytogenetics, and that the requisite tissue and data banks will be developed to provide the specimens necessary for these studies.

Chapter 6 (T. Krontiris)

Oncogenes, a class of growth-regulating genes, have been identified as major participants in the process of malignant transformation and the types of somatic mutations that activate them in cancer cells, such as rearrangements, point mutations and amplifications, have, in many cases, been analyzed in great detail. This detailed understanding of the oncogene role in carcinogenesis has led to several studies in which rare RFLPs of particular oncogenes have been found to be associated with particular cancers. For example, in one study, a rare RFLP of *c-mos* was present in six breast cancer patients, one leukemia patient and none of the 69 controls. One of the most thoroughly examined oncogene RFLPs is the HRAS1 locus, which contains a variable tandem repeat (VTR) of a 28 base pair (bp) consensus sequence located about one kb downstream from the *H-ras* oncogene. RFLPs of HRAS1 are generated by variations in the number of repeat units comprising the VTR. There are four common alleles, a1 through a4, which account for 92% of the total;

they range in size from 1,000 bp (a1) to over 2,500 bp (a4). The more than 20 rare alleles, ranging in size from 850 bp to greater than 3,000 bp, occur with frequencies ranging from 0.06 to 2.0%. The function and origin of VTRs are obscure, although there is some evidence suggesting that they may act as enhancers or as origins of DNA replication. They are typically unstable and have high rates of mutation. Several studies now have shown that the rare alleles of HRAS1 occur at much higher rates among cancer patients than among controls and that HRAS1 may be useful as a predictor of cancer risk.

The reasons for the association between cancer and the rare alleles are unclear but are under active investigation. Studies of familial melanoma and breast cancer have shown that although rare HRAS1 alleles are increased in these families, there is no linkage between the rare alleles and the cancers. These results suggest that the presence of rare alleles may be a secondary pathogenetic influence that works in conjunction with other primary disease loci. One possibility is that rare alleles arise as a result of some type of genetic instability, such as replication slippage or an enhanced rate of gene conversion. Sequence analysis of HRAS1 alleles and RFLP analysis within the HRAS1 locus using additional restriction endonucleases leads to the conclusion that the rare alleles arise from the common alleles nearest them in size, a result consistent with replication slippage or gene conversion but not with unequal crossing-over. The increased incidence of rare alleles in cancer patients might thus reflect a generalized increase in genetic instability that predisposes to cancer. If this is the case, then other VTRs that are dispersed throughout the genome should reflect the same tendency. Many questions about the structure and function of VTRs and their association with disease remain unanswered and require further research for their elucidation.

Chapter 7 (T. Roderick)

The advances of the past few years in DNA technology have permitted an unprecedented growth in our knowledge of the detailed structures of DNA of many organisms, from viruses to bacteria to homo sapiens. One of the most remarkable facts that has emerged is that there is a high degree of homology and conservation of genetic structure among organisms and particularly among the mammals. The homology pertains not only to coding segments of genes, but also to the order of genes on chromosomes. For example, mice and humans, although evolutionarily separated for about 65 million years, have at least 45 homologous autosomal segments, involving over 350 genes, as well as overall homology of both the X and Y chromosomes. In the mouse, more than 2,600 loci, including DNA polymorphisms and other chromosomal markers, are now known, of which 1,600 have been mapped to specific chromosomal locations. Because of the extensive homology between human and murine genomes, and with the existence of increasingly detailed comparative chromo-

some maps of these two species, it is now possible to infer the existence, structure and location of human genes from their murine counterparts with increasing confidence.

This comparative approach to gene localization has been particularly useful for cancer-related genes, such as proto-oncogenes. A sizable body of evidence demonstrates that activation of these growth- and differentiation-controlling genes, by point mutation, chromosomal rearrangement, amplification or retroviral modification and insertion, contributes to oncogenesis. Activated oncogenes have been found in many human tumors and insertion of activated oncogenes into non-malignant cell lines can lead to malignant transformation. Although other genes (eg, antioncogenes) may also be involved in the process, there is overwhelming support for the centrality of oncogenes in carcinogenesis. Much of our current knowledge of these genes is derived from murine studies. Of the 2,600 known murine genetic loci, 349 are proto-oncogenes and related cancer genes. The high proportion (about 15% of the total) of cancer-related genes may reflect the fact that a large number of genes are required for regulation of growth and differentiation, or perhaps that because they are of intense scientific interest, these genes have been sought out more avidly than others.

The comparative map of human and mouse chromosomes, with gene homologies, proto-oncogenes and other cancer-related genes clearly indicated, comprises the bulk of this chapter. With the data presented in this manner, one can take maximal advantage of the known homologies between the species and can use the cancer-related genes in the mouse to predict the location and function of homologous human loci. It is among these cancer-related genes that one can most profitably look for those that are most likely to be involved in the predisposition to cancer. With progress in the mapping of both human and murine chromosomes proceeding rapidly, we expect that comparative maps of the type presented here will become increasingly detailed and useful.

Chapter 8 (M. Rothstein)

A broadly available program to detect cancer predisposition, if undertaken with increased surveillance of those at risk and with recommendations for life style changes and avoidance of appropriate exposures, might lead to significant improvement in early cancer detection, cure and prevention. Although this clearly would be beneficial to society it would bring with it many difficult legal and ethical issues. While it is impossible to be comprehensive and detailed here about all the issues raised by our ability to detect persons at increased risk of cancer, we must consider the following:

- 1) Whether there is a medical/legal/ethical obligation to disclose test results to family members, who may share the predisposing genes, without the permission of the patient. This is especially relevant if the

presence of a particular predisposing gene would result in a life-preserving intervention.

- 2) Under certain conditions, testing for cancer predisposition might be mandated by public health officials in schools or the military, much as vision and hearing screening is now done. This might bring with it mandatory risk reduction programs, such as prohibition of smoking by high-risk individuals in the military or mandatory diet restrictions, and might lead to stigmatization of, and discrimination against, affected individuals.
- 3) Many issues arise in reproduction. Genetic screening of fetuses for their cancer predisposition might become feasible and might influence abortion decisions. Neonatal screening might be required if effective early interventions would prevent the expression of the predisposition. If testing becomes widespread, individuals engaging in sexual intercourse might have a legal duty to inform their partners about their genetic profiles. They might otherwise risk liability for fraud, negligence or other torts.
- 4) Screening for cancer predisposition would have significant impact on health and life insurance. Health insurers might be interested in excluding from coverage or eliminating cancer coverage for those predisposed. Life insurance would also be expected to include cancer predisposition among the risk factors used in setting rates.
- 5) In the area of employment, identification of cancer-predisposed workers could lead to discriminatory hiring practices and/or mandatory job assignments to avoid potential carcinogen exposures.

Although the issues likely to emerge with testing for cancer predisposition are bound to be difficult, there is no question that such testing doubtless will be developed. This argues for the simultaneous development of thoughtful social policies and legislation so as to minimize the dislocations wrought by the scientific advances.

SUMMARY RECOMMENDATIONS

1. The complexities of drug metabolism and the frequent occurrence of polymorphisms make it necessary to continue efforts to characterize both the genes and enzymes involved in these pathways and their patterns of expression, so that the mechanisms of variability of drug and carcinogen susceptibility can be understood. Cell lines containing cloned human drug-metabolizing enzymes should be developed for use in screening, to permit more accurate assessment of human toxicity, carcinogenicity and mutagenicity of chemicals. Techniques for in vivo phenotyping and genotyping of human populations

need to be further developed, and where possible, lymphocyte DNA-based methods for detecting mutant drug-metabolizing enzymes should be devised.

2. The acetylator phenotype (and genotype) is a stable individual characteristic that can be determined relatively easily by urine testing after caffeine ingestion. The phenotype has been implicated as a modulator of susceptibility to several types of cancer. It is suggested that acetylator status determinations be incorporated into appropriate, prospective epidemiologic studies of human breast, bladder, colorectal and gastrointestinal cancers to test the validity of the putative associations of acetylator status with the diseases. Characterization of the acetylator genes should be pursued with an eye to the development of simpler techniques for genotyping individuals based on lymphocyte DNA analysis. Development of experimental systems in which acetylator genes can be placed in different genetic backgrounds should be encouraged for the insights they can provide into polygenic modes of inherited cancer susceptibility.

3. Since susceptibility to environmental agents seem likely to arise from the complex interaction of activating and inactivating drug-metabolizing enzymes, efforts should be focused on the correlation of cancer predisposition with multi-enzymic patterns of carcinogen and drug disposition.

4. Fragile sites, common chromosomal sites which are predisposed to breakage under a wide variety of stimuli, are frequently also the locations at which the translocations and deletions associated with cancer occur. They are sites of genomic instability that may arise from particular classes of "sensitive" DNA sequences and/or from "exposed" chromatin structures. Characterization of the DNA sequences and chromatin structure at these sites is recommended to clarify their relationship to cancer predisposition.

5. The chromosome-breakage syndromes, six distinct clinical entities, are characterized by genetic instability and cancer predisposition. Although most of them can be distinguished by the appropriate battery of cytogenetic tests, the laboratory diagnosis of xeroderma pigmentosum (XP) is not completely satisfactory and would be improved by development of a test for excision-defective repair that could be performed on lymphocytes and by an easier method for complementation group assignment. For all of these diseases, methods of identifying heterozygotes are of special importance as they will permit studies of cancer predisposition in unaffected gene carriers. It is likely that such methods will be developed when the defective genes are cloned and characterized. It should then be possible to define more exactly the roles played by the affected genes and proteins in the maintenance of the structural integrity of DNA. The importance of registries of persons affected with these diseases should be recognized: they are efficient, inexpensive means of learning about and facilitating treatment of rare conditions.

6. Epidemiologic studies of various designs have confirmed the existence of genetic predisposition to cancer. Further studies would be facilitated by a multidisciplinary approach that incorporates molecular/genetic markers and probes, genetic polymorphisms and other clinical and genetic data. The establishment of a population-based data- and tissue-bank collected from individuals with various types of cancer could serve as an invaluable resource in this work.

7. Hypervariable minisatellite DNA sequences (VTRs) are genetically unstable structures, present throughout the genome, that may serve as origins of DNA replication or transcription enhancers. For one of them, the *HRAS1* locus, it has been shown that rare allelic forms occur far more frequently in patients with many types of cancer than in controls. The role and function of VTRs in cancer predisposition may be investigated in several ways. Large studies of specific cancers need to be performed to see if rare alleles cluster among particular cancer types. The VTR system can be examined for possible influences of environmental exposures, especially in lung and bladder tumors for which several environmental risk factors are known. Family studies of VTRs, in which the linkage of rare alleles to familial forms of cancer are investigated can show whether a genetic relationship exists between VTRs and particular tumors. VTRs, because of their instability, can be used to assess mutation rates in families with strong positive and negative cancer histories, to see if any differences are present. VTRs associated with oncogenes other than *Hras* should also be sought.

8. The continuing rapid pace of gene mapping in both murine and human genomes has uncovered a considerable degree of homology between the species. A large number of "cancer-related" genes have been identified in the mouse and, because of the homologies between the species, human counterparts may be expected. The Study Group recommends a continuation of mapping and comparative studies as a means of uncovering genes that may predispose to cancer.

9. As social and ethical consequences are likely to result from utilization of tests to detect cancer predisposition, the Study Group recommends that development of rational policies and guidelines for their use occur prior to, or simultaneously with, the implementation of the tests.

CHAPTER 1

Hereditary Polymorphisms of Human Drug Metabolizing Enzymes and Cancer Susceptibility

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I. ROLE OF DRUG METABOLIZING ENZYMES IN CHEMICAL CARCINOGENESIS

It has long been recognized that the environment plays a major role in the etiology of cancer. In addition to ultraviolet light, environmental contaminants and dietary substances have been shown through the years of experimentation using animal models to be significant determinants in the process of carcinogenesis. Undoubtedly, genetics also has a role to play in determining susceptibility to chemical carcinogenesis. For example, only one in five smokers develops lung cancer. The differences in susceptibility among smokers could be due to genetic polymorphisms in oncogenes, tumor suppressor genes or immuno surveillance mechanisms; they may also arise from differences in drug metabolizing enzymes that have profound effects on the way chemical carcinogens are handled in the body.

Over 30 years ago the Millers demonstrated that chemical carcinogens are usually chemically inert substances that require metabolic activation to high energy intermediates capable of damaging cellular macromolecules such as DNA (reviewed in Miller and Miller, 1976). Alternatively, toxic and mutagenic chemicals may be inactivated by cellular enzymes. The enzymes involved in carcinogen metabolism can, therefore, either be beneficial—producing inert metabolites—or harmful—generating reactive intermediates. The cellular complement of drug metabolizing enzymes, therefore, likely governs whether the chemicals to which an animal is exposed are inactivated and eliminated or activated to DNA damaging intermediates.

The drug metabolizing enzymes have been found to be highly polymorphic in humans and animals. In mice, polymorphism in the regulation of a single carcinogen-activating enzyme can render different strains susceptible or resistant to chemical carcinogenesis (Nebert, 1986). Because of their role in carcinogen activation/inactivation and their propensity toward polymorphic expression, the drug metabolizing enzymes are prime candidates for genes predisposing humans to risk of cancer. This chapter will focus on the biochem-

istry, evolution and polymorphisms of the phase I cytochrome P450s. Other drug metabolizing enzymes, including those involved in phase II conjugation reactions, will also be discussed briefly. Finally, recommendations will be presented to guide future areas of investigation into the role of these enzymes in cancer susceptibility.

II. CYTOCHROME P450s

A. Physical, Chemical and Enzymologic Properties

Two primary classes of P450s exist, both of which are membrane-bound: one localized to mitochondria, the other to microsomes. Both classes range in molecular weight between 50,000 and 60,000 daltons, contain a noncovalently bound heme (protoporphyrin IX) that associates with a region of the protein near to the carboxy terminus, and receive electrons from NADPH (sometimes NADH) via a second flavin containing enzyme. The flavoprotein transfers electrons to mitochondrial P450s by way of the iron-sulfur protein adrenodoxin. The microsomal P450s, on the other hand, receive electrons directly from the flavoprotein NADPH-P450 oxidoreductase. Electrons and O_2 are used in the substrate oxidation process with the byproduct being H_2O . The other fundamental difference between the two classes of P450s is their mechanism of insertion into membrane, which directs the placement of the polypeptide into the appropriate intracellular compartment. The membrane localization of P450s is ideally suited to the hydrophobic nature of many substrates. These substrates will dissolve in the intracellular lipid bilayers prior to being converted to more hydrophilic derivatives by P450.

Mitochondrial P450s have evolved to carry out highly specialized reactions that are associated with steroid biosynthetic pathways such as the synthesis of cortisol, aldosterone, and vitamin D_3 . These enzymes are primarily expressed in highly specialized tissues such as the adrenal, ovary, testis, and kidney.

The microsomal P450s are, on the other hand, the principal enzymes involved in metabolism of foreign compounds. A few of them also may carry out critical oxidations of endogenous substances. The foreign compound-metabolizing P450s are highly concentrated in liver although many of them are expressed to some extent in extrahepatic tissues such as lung, kidney and intestine. Many P450s, however, are restricted to the liver, and it is in this tissue where the bulk of oxidation occurs.

The purification and properties of P450s from rats, rabbits and man have been reviewed (Guengerich, 1987). Within a given organism up to 15 forms of P450 have been purified and studied. The enzymatic specificities of purified preparations of P450 have been assessed using reconstitution assays. These assays consist of purified P450, NADPH-P450 oxidoreductase and artificial

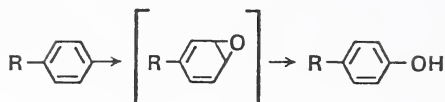
lipid, usually dilaurylphosphatidylcholine. In some cases cytochrome b_5 , which can act as the conduit for the low redox potential electron, is added to the reconstituted system. Substrates are added in the presence of NADPH and the reactions are allowed to proceed under atmospheric oxygen. Oxidized products are then analyzed by various analytical techniques, such as thin layer chromatography, high pressure liquid chromatography, UV, visible and fluorometric spectroscopy, gas chromatography and mass spectrometry. The reactions proceed via an oxygen-activated iron in a two-electron transfer process. A single atom of oxygen is inserted into the substrate while the other oxygen is converted to water. During the P450 catalytic cycle many compounds form unstable intermediates that can rearrange to produce a particular product. Among the reactions catalyzed through P450-mediated oxidations are aliphatic and aromatic hydroxylations, epoxidations, N, C, and O dealkylations, deaminations and reductive dehalogenations (Fig. 1). Frequently, the high energy intermediates formed by P450 can produce cytotoxicity and mutations.

One of the most unique aspects of the P450 monooxygenase system is its capacity to metabolize scores of substrates of different structures and physicochemical properties. It is clear that probably only from 30 to 50 distinct forms of P450 may be expressed in liver. Each form, however, is capable of metabolizing a large number of substrates. Some forms will primarily oxidize arylamine-type compounds while other forms will oxidize polycyclic aromatic hydrocarbons. The reason for the broad substrate specificities of P450s may be that they have loose substrate binding sites. For instance, a substrate may enter the active site and diffuse until it contacts the important catalytic residues. This is apparent when examining oxidation of steroids (catabolic pathways of questionable physiologic relevance). A particular steroid such as testosterone can be hydroxylated at up to eight different positions on the molecule (Matsunaga et al, 1988). The loose active sites probably result in the notoriously low substrate turnover numbers, which range from less than 1 to 50. This compares to several thousand for typical enzymes involved in intermediary metabolism.

It is important to note that the affinities of P450s for different substrates vary significantly. A given P450 may have a high affinity (low K_m) for a given substrate *A* and a low affinity (high K_m) for substrates *B*, *C*, and *D*. Therefore, given a low dose of substrates *A*, *B*, *C*, and *D*, the animal may only metabolize *A*. With higher doses, this P450 may metabolize all four substrates. If the animal lacks the P450 for substrate *A*, *A* will not be metabolized unless other forms of P450 are present that can catalyze the oxidation of *A*. This property of P450s underscores the caution that must be observed when analyzing human drug and carcinogen metabolism.



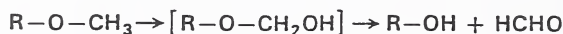
ALIPHATIC OXIDATION



AROMATIC HYDROXYLATION



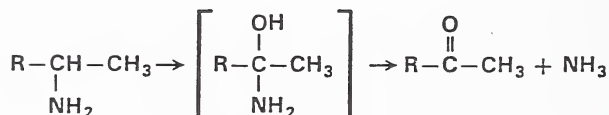
N-DEALKYLATION



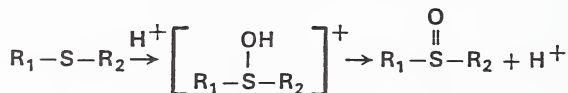
O-DEALKYLATION



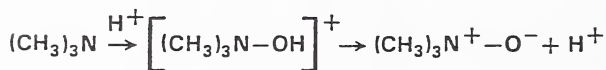
S-DEALKYLATION



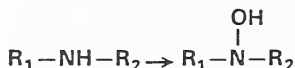
OXIDATIVE DEAMINATION



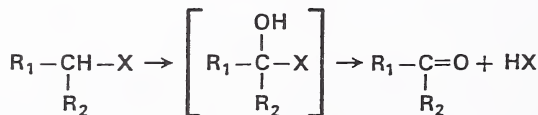
SULFOXIDE FORMATION



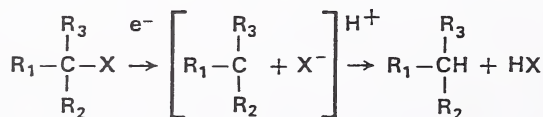
N-OXIDATION



N-HYDROXYLATION



OXIDATIVE DEHALOGENATION



REDUCTIVE DEHALOGENATION

Fig. 1. A summary of some P450-mediated reactions. The unstable intermediates are enclosed by brackets.

Pharmacologists have long recognized that intra- and interspecies differences exist in drug metabolizing enzymes. A certain chemical can be highly toxic to one species and safe in another species. In addition, substrains of a given species can show dramatic differences in drug oxidation reactions. This is most notable in mice (Gonzalez, 1988). The molecular basis of these differences can be explained by the evolution of the P450 genes (see below). These observations create problems and introduce interesting possibilities for models to use in studying human response to environmental chemicals. For example, since the P450s can be different between rodents and man, caution must be exercised when rodents are used to test the toxicity and carcinogenicity in humans of foreign chemicals. Can rodent data be extrapolated to man? The *intraspecies* differences noted in rodents further suggest that individuals may differ in their susceptibility to toxins and carcinogens. Indeed, drug oxidation polymorphisms are common in man. Again, as mentioned earlier, it may be possible to predict susceptibility to the untoward effects of chemicals by measuring individual levels of P450s.

B. Molecular Biology and Evolution

P450s are collectively grouped into a gene superfamily consisting of 13 gene families including 8 families in mammals, 1 in chicken, 2 in yeast, and 2 in bacteria. Other P450 families, undoubtedly, have yet to be discovered. The delineation of P450 gene families is based solely on amino acid sequence relatedness. P450 families display less than 35% to 40% sequence relatedness. Within several of the gene families, subfamilies exist that display from 40% to 60% amino acid similarities. The P450 gene families have formed such a long time ago that they are located on seven different human chromosomes (Table 1).

TABLE 1. Chromosome Locations of P450 Gene Families in Man*

Family	(Subfamily)	Location
<i>CYP1</i>	(A)	15q22-qter
<i>CYP2</i>	(A)	19q13.1-13.2
	(B)	19cen-q13.3
	(C)	10q24.1-24.3
	(D)	22q11.2-qter
	(E)	10
	(F)	19
<i>CYP3</i>	(A)	q21.3-q22
<i>CYP4</i>	(B)	1
<i>CYP11</i>	(A)	15
<i>CYP17</i>		10
<i>CYP19</i>		15
<i>CYP21</i>		6p

*Data taken from Nebert et al (1989) and references therein.

In mammals five P450 gene families, designated *CYP11*, *CYP17*, *CYP19*, *CYP21*, and *CYP26*, are involved in steroidogenic pathways. These include both the mitochondrial type and the microsomal type of P450s and, as mentioned earlier, these enzymes are expressed in highly specialized tissues. The *CYP4* family codes for P450s that metabolize fatty acids such as laurate, arachidonate, and prostaglandins. The remaining gene families designated *CYP1*, *CYP2* and *CYP3*, code for enzymes involved in the metabolism of foreign compounds. The number of P450 genes currently known to exist in each family in rat and man is shown in Table 2. These data demonstrate the quantitative differences in P450 genes between these two species, as discussed above.

The *CYP1* family contains two genes that are found in both rodents and man. The IA1 protein can actively metabolize various polycyclic aromatic hydrocarbons and is also capable of activating many of these compounds to mutagenic metabolites (Aoyama et al, 1989b). The IA2 enzyme is involved in metabolism of many aromatic amine compounds, including the potent promutagen heterocyclic arylamines derived from pyrolysates of proteins. This enzyme is responsible for converting several potent arylamine carcinogens to their activated forms (Table 3). The IA2 is constitutively expressed in hepatocytes but is not found in extrahepatic tissues. IA1 is not expressed in the

TABLE 2. Number of P450s in Four Gene Families in Rat and Man¹

Family	(Subfamily)	Number of P450 Genes	
		Rat	Man
<i>CYP1</i>	(A)	2	2
<i>CYP2</i>	(A)	3	3
	(B)	5	3
	(C)	5	2
	(D)	5	3 ²
	(E)	1	1
	(F)	ND	1
	(G)	ND	1
<i>CYP3</i>	(A)	2	4
<i>CYP4</i>	(A)	3	>1 ³
	(B)	1	1

¹These data taken from Gonzalez (1988) and Nebert et al (1989) and represent the minimum number of genes or P450s found to date. These estimates are primarily based on cDNA and gene cloning.

²One of these genes is a pseudogene and one is inactive or mutant in caucasians (~40% allele frequency). The third gene may not be expressed in human liver (unpublished experiments).

³Based on Southern blotting experiments it appears that multiple genes probably exist in man although only a single cDNA has been isolated.

TABLE 3. Carcinogens and Mutagens Activated by IA2

Carcinogens and Mutagens ¹	Mutagens ²
2-Aminofluorene	Glu-P-1
2-Acetylaminofluorene	Glu-P-2
4-Aminobiphenyl	Trp-P-1
2-Aminoanthracene	Trp-P-2
Benzo(a)pyrene 7,8-dihydrodiol	IQ
	IQx
	MeIQ
	MeIQx

¹Known to be both carcinogenic and mutagenic in man or rodents.

²Not conclusively shown to be carcinogenic in man or rodents.

absence of inducing agents including polycyclic aromatic hydrocarbons and 2,3,7,8-tetrachlorodibenzo-p-dioxin. IA2 is also induced by these compounds.

The *CYP3* gene family consists of at least 2 genes in rodents and 4 genes in man. At least one of these genes in each species is activated by synthetic steroids such as dexamethasone and pregnenolone 16 α -carbonitrile. These P450s can metabolize several clinically important drugs including the antibiotics triacetyloleandomycin (TAO) and erythromycin, the tranquilizer midazolam, and the immunosuppressant cyclosporine. Recently it was reported that a form or forms of human P450 in the *CYP3* family is responsible for activating aflatoxin B1 to its mutagenic metabolite (Shimada and Guengerich, 1989). Other carcinogens activated by one or more P450s in the *CYP3* family include 6-aminochrysene and aflatoxin G1. Enzymes in this family in humans are expressed to varying degrees between individuals (Gonzalez et al, 1988).

The *CYP2* gene family is the largest family of genes in mammals. Seven subfamilies, designated *CYP2A* through *CYP2G* have been uncovered in mammals. The number of genes within a particular subfamily ranges from one to five depending on the species. Several of these subfamilies are very different in composition and in their activities between species. In addition, genes in the *CYP2C* and *CYP2D* subfamilies are known to be polymorphically expressed in man (see below). The P450s in the various *CYP2* gene subfamilies are the primary enzymes involved in the oxidation of foreign compounds. Guengerich (1987) has reviewed many of the drugs and toxins that are metabolized by P450s in rodents and man. Several of these enzymes are also inducible by agents such as phenobarbital and 3-methylcholanthrene.

Major differences are found between the P450s expressed in rodents and man, especially those in the *CYP2* family (Table 2). Although the subfamilies can be clearly distinguished it becomes very difficult to determine orthologous counterparts between species. For instance, it is impossible to tell which of the

five rat *CYP2C* genes corresponds to the two human *CYP2C* P450 genes. Moreover, the catalytic activities of the latter two human P450s appear distinct from the five rat enzymes. Even when the orthologues can be discerned, based on high amino acid similarities, the enzymes may still have distinct catalytic activities and regulatory patterns. For instance, the IIA3 P450 is found in rat, mouse, and man, yet this gene is under distinct regulatory control in each species (Kimura et al, 1989). The rat IIA3 is expressed in lung and not in liver or kidney, while mouse IIA3 is expressed in liver and kidney. Human IIA3, on the other hand, is not expressed in lung but is expressed in liver. These data uniquely illustrate the interspecies differences in P450 expression and further underscore the caution that must be observed when extrapolating carcinogenesis data from rodent to man.

Finally, and most importantly, intraspecies differences in P450 expression have been well documented. In rabbits a genetic polymorphism exists in P450 IIC5 that codes for progesterone 21-hydroxylase activity (Dieter et al, 1982). A genetic defect has also been described in the rat *CYP2D1* gene (A1-Dabbagh et al, 1981). Multiple genetic defects in P450 expression have been described in mice, including the well known "Ah locus" polymorphism that is manifested by the lack of induction of IA1 in several strains of mice (Nebert, 1986).

The question arises as to why so many genetic differences exist in P450s both between and within species. It was proposed that the driving force behind the evolution of P450 genes has been diet, in particular the consumption of plant toxins (Nebert and Gonzalez, 1985; Nelson and Strobel, 1987). This is primarily based on examining the phylogenetic trees of P450s and correlating the enzymatic activities of P450s with their estimated times of formation (Fig. 2). It appears that early P450s were those that metabolized lipids and steroids while the more recently evolved P450s metabolized foreign compounds. The emergence of P450s in the *CYP2* family about 400–600 million years ago coincides with the emergence of land animals from an aquatic environment at a time after the adaptation of terrestrial plant life. The P450s were probably needed to detoxify plant toxins. Hence, as each species developed in its own habitat, it needed a distinct battery of P450s to nullify the toxins contained in the plants from which it fed. Species-specific diets may be responsible for the species-specific P450 expression and activities. As diets change certain P450s can be dispensed with and through lack of selective advantage, certain P450s may be lost in a population, giving rise to intraspecies P450 genetic defects. These defects, however, are not lethal. This property separates P450 molecular genetics from all inborn errors of metabolism that usually mean sickness and/or death. The possibility that genetic differences in P450 gene expression

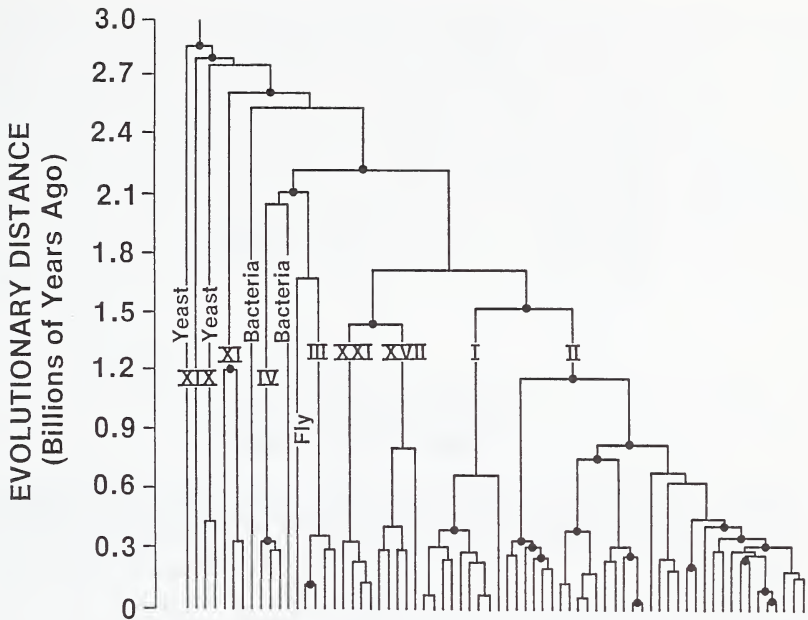


Fig. 2. A phylogenetic tree of the P450 gene superfamily. These data were derived as described in Nelson and Strobel (1987). The divergence values are calculated from comparisons of the primary amino acid sequences of the individual P450s and the speciation times of various organisms. The two bacterial, two yeast and fly families are shown in the Figure. The remaining nine families are found in mammals.

account for susceptibility or resistance to cancer is only beginning to be realized.

III. HUMAN POLYMORPHISMS IN DRUG OXIDATIONS

A. Definitions and General Characteristics

The term polymorphism, which is defined as "many forms and the occurrence in the population of two or more genetically determined phenotypes," has been used to describe drug oxidation defects. Polymorphisms can refer to any inherited genetic traits, such as coat color in a mouse, different electrophoretic forms of enzymes synthesized by different alleles of the same gene or even restriction fragment length polymorphisms or RFLPs. In clinical pharmacology, a drug oxidation polymorphism refers to the differential ability of a population of subjects to metabolize a drug. A drug oxidation polymorphism is

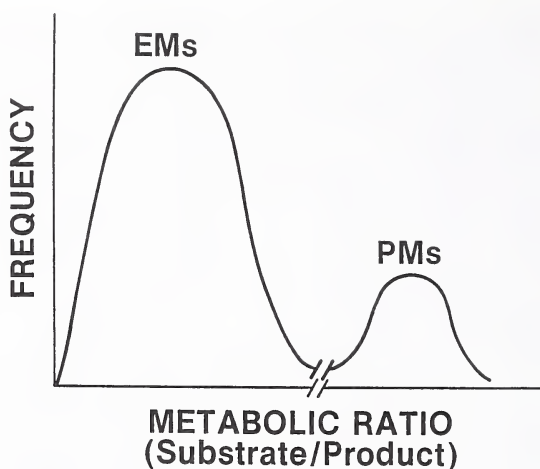


Fig. 3. A schematic chart showing an ideal bimodal distribution indicating a possible drug oxidation polymorphism. Extensive metabolizers (EMs) and poor metabolizers (PMs) are represented by low and high metabolic ratios, respectively.

characterized by a bimodal distribution of oxidation phenotypes typified by those that can actively metabolize a drug and those that cannot (Fig. 3). Further, the inability to metabolize a drug should be an inherited trait. Individuals who cannot metabolize a drug have been termed "poor metabolizers" or PMs while those who can metabolize a particular drug are termed "extensive metabolizers" or EMs. This is usually established through family studies. Assuming a single genetic defect that is homozygous recessive, the ideal pattern of a drug oxidation polymorphism would be a trimodal distribution of metabolism including the deficient metabolizers (two copies of a defective allele), a normal metabolizer (two copies of a normal allele), and an intermediate metabolizer (one copy of the normal and one copy of a mutant allele). In practice, however, a trimodal distribution is rarely seen.

The discovery of two of the well-established human drug oxidation polymorphisms, (one for mephenytoin, the other for debrisoquine), was rather serendipitous. Only retrospective analysis revealed that the problems associated with the clinical use of debrisoquine were due to a drug oxidation deficiency, which rendered some individuals exquisitely sensitive to its actions. Subsequently numerous studies have examined the metabolism of other drugs in human populations and many have been found to suffer the same deficient metabolism as debrisoquine. All of these drugs are metabolized by the same cytochrome P450 IID1, which has overlapping substrate specificities, and which exists in aberrant nonfunctional forms in many individuals (see later).

The ability to detect impaired drug oxidation is a function of the pharmacokinetics of a drug and the assay method used for metabolite detection. Ideally the drug should be oxidized and eliminated in a simple fashion (eg, a simple hydroxylation and quantitative excretion of both parent compound and metabolite in the urine). However, more frequently a particular compound can be metabolized at several positions and also conjugated with either glucuronic acid, sulfate or glutathione. These types of derivatives are sometimes excreted in bile. Excretion in urine is absolutely critical for studies involving large populations. It becomes more difficult to collect specimens when serum levels need to be assayed.

B. The Mephenytoin Polymorphism

1. Clinical pharmacology. Mephenytoin is an anticonvulsive agent. The S-enantiomer of the drug is metabolized by hydroxylation at the 4 position and this hydroxylation reaction results in its inactivation. The R-enantiomer is demethylated but the demethylated product has similar anticonvulsive properties to the parent drug. The human genetic polymorphism in the production of the S-mephenytoin 4' hydroxy metabolite was firmly established by Kupfer and Preisig (1984).

The most common means of measuring mephenytoin metabolism is to administer a single oral dose in tablet form and measure the excretion of the 4' hydroxy metabolite after hydrolysis of its glucuronic acid conjugate. The mephenytoin metabolites have been measured by capillary gas chromatography and gas chromatography-mass spectrometry. A variety of methods have been developed to achieve an accurate assessment of hydroxylation efficiency. The problems associated with measuring mephenytoin metabolism have been discussed (Wilkinson et al, 1989). The most successful approach is the "hydroxylation index" (Kupfer and Preisig, 1984) or the molar ratio of administered drug to level of excreted 4' hydroxy metabolite in a 0 to 8 hour urine sample. This index is most accurate when drug absorption is controlled for by the simultaneous measurement of a second unrelated metabolite. For example, it is common to administer mephenytoin and debrisoquine in a single tablet and to measure the metabolism of both drugs.

The frequency of poor metabolizers, PMs, of mephenytoin is about 2% in North American and European caucasians. In orientals, the frequency of PMs is much higher, at about 18% to 25% (Nakamura et al, 1985; Ward et al, 1987). In a tribe of Central American Indians no PMs were found in 90 individuals (Inaba et al, 1988). These studies indicate the striking ethnic differences in drug oxidation polymorphisms.

2. The molecular basis of the defect. A P450, designated P450_{MP}, having S-mephenytoin 4'-hydroxylase activity was purified from human liver (Shimada et al, 1986). The cDNA for P450_{MP} (IIC9) was subsequently cloned

(Umbenhauer et al, 1987) and its sequence revealed that this enzyme was a member of the *CYP2C* subfamily. Two other related cDNAs were isolated and found to share significant sequence similarities with IIC9 (Okino et al, 1987; Ged et al, 1988). It is still unclear how many closely related genes exist in the human *CYP2C* subfamily; at least five are known to exist in rat. No mutant genes have been found for P450_{MP} (IIC9) and immunoblot analysis of human liver specimens have failed to produce evidence for a missing P450 in livers that lack S-mephenytoin 4'-hydroxylase activities (Umbenhauer et al, 1987; Meier and Meyer, 1987). This is undoubtedly due to the presence of multiple immunochemically related *CYP2C* gene products. Further, no biochemical means exist to identify poor metabolizers by analysis of lymphocyte DNA.

C. The Debrisoquine Polymorphism

1. Clinical pharmacology. Debrisoquine is an adrenergic blocking agent developed as a means to control blood pressure. This drug has been used in Europe, was never approved for use in the United States, and has not gained widespread use due to its toxicity in a significant number of patients. Debrisoquine is inactivated by a P450 mediated hydroxylation at the 4 position of the molecule. The parent compound and its metabolite are secreted in the urine and the hydroxy derivative is unconjugated. It was found that individuals for whom this drug is toxic have an impaired ability to metabolize debrisoquine (Mahgoub et al, 1977). The frequency of PMs range from between 5% and 10%, in the white populations of Europe and North America. Interestingly, Oriental subjects are virtually all EMs (Nakamura et al, 1985). Again it is clear that important racial differences exist in drug metabolizing enzymes. A human deficiency in metabolism of the β -blocking drug sparteine has been independently studied (Eichelbaum et al, 1979) and found to fall into the debrisoquine defect category (Eichelbaum, 1986).

In addition to debrisoquine, a number of other drugs are subjected to the same polymorphic distribution. These studies were carried out by comparing populations of individuals for their ability to metabolize debrisoquine and other drugs. For instance, 4 hydroxylation of the hyperglycemic drug phenformin was found to be impaired only in individuals who could not metabolize debrisoquine (Shah et al, 1985). The antianginal agent perhexiline is also subjected to polymorphic oxidation and follows the same distribution as debrisoquine (Shah et al, 1983). Patients who received this drug and who developed serious side effects such as peripheral neuropathy were found to be PMs. These data suggest that debrisoquine, phenformin and perhexiline are metabolized very specifically by a single P450 that is deficient in a significant number of individuals.

2. Molecular basis of the defect. A P450 that metabolizes debrisoquine, designated IID1*, was isolated from rats (Larrey et al, 1984; Gonzalez et al, 1987) and man (Distlerath et al, 1985; Gut et al, 1986). The rat (Gonzalez et al, 1987) and human (Gonzalez et al, 1988a) debrisoquine 4-hydroxylase cDNAs were also cloned and sequenced. The *CYP2D* subfamily was mapped to human chromosome 22 using the cDNA probe. Studies using highly specific antibodies to IID1 revealed that humans incapable of metabolizing debrisoquine or the prototype substrate bufuralol did not possess the IID1 protein (Gonzalez et al, 1988b). Direct cloning of mutant gene transcripts from these livers revealed the presence of variant IID1 mRNAs produced by defective *CYP2D6* alleles. The transcripts cannot produce a normal P450. Other studies using the cDNA probe in conjunction with RFLP analysis of lymphocyte DNA revealed that up to 70% of the mutant *CYP2D6* alleles could be detected by this procedure. The remaining 30% of the defective alleles could not be distinguished.

D. Other Potential P450 Polymorphisms

1. P450 IA1. IA1 is the principal P450 involved in the metabolism and activation of polycyclic aromatic hydrocarbon carcinogens. This is a unique P450 since it is found in a variety of different organisms including fungi, birds, fish, frogs and mammals. In addition, IA1 is expressed in a large number of tissues including liver, lung, kidney, intestine, brain and skin. Its expression, however, is totally dependent on the presence of an appropriate inducer. Among the inducers of *CYP1A1* gene expression are multiple polycyclic aromatic hydrocarbons, such as benzo(a)pyrene and benz(a)anthracene and the environmental contaminant 2,3,7,8-tetrachlorodibenzo-p-dioxin. In the absence of these agents IA1 is not found in any tissue.

IA1 has been implicated as playing a major role in polycyclic aromatic hydrocarbon carcinogenesis in rodents (Nebert, 1986). Its role in man is unclear, however. The enzyme has been detected in the placenta of smoking mothers (Song et al, 1985) and in lymphocytes that had been cultured with mitogens and inducers (Kellerman et al, 1973; Levine et al, 1984). In a recent study, levels of IA1 associated benzo(a)pyrene hydroxylase activities, measured by the extents of induction of activity in mononuclear lymphocytes, varied up to about 15-fold and a trimodal distribution was obtained (Yamashita et al, 1989). The predicted frequencies for homozygous high inducibility, homozygous low inducibility and heterozygotes was 0.10, 0.36 and 0.54, respectively. These data suggest that inducibility might be inherited in humans, but is not as clear as the inherited deficiency in mice (Nebert, 1986).

*According to the new P450 gene nomenclature system, the rat and human debrisoquine 4-hydroxylase genes are designated *CYP2D1* and *CYP2D6*, respectively (Nebert et al, 1989). The proteins and mRNA for this enzyme are still designated IID1 for simplicity.

No method has been developed to detect IA1 expression or activities by urine metabolite analysis or by RFLP analysis. It is possible that mutations in the *CYP1A1* structural gene may not be found in man. More likely, genetic differences may be found in the other factors required for IA1 inducibility.

2. P450 IA2. IA2 is involved in the activation of several arylamine carcinogen and heterocyclic arylamine mutagens. This enzyme is also capable of metabolizing numerous drugs including theophylline, phenacetin and caffeine. In contrast to IA1, IA2 is constitutively expressed in liver and is absent in extrahepatic tissue. In rodents, IA2 is inducible by the same compounds that induce IA1. It is not known whether IA2 is induced in human liver; however, variable levels of this P450 have been found in different human liver specimens (Wrighton et al, 1986).

A caffeine breath test has been developed that measures a P450 mediated N-demethylation of isotopically labeled caffeine (Renner et al, 1984; Lambert et al, 1986). Rodent studies suggested that IA2 was the cytochrome responsible for the reaction (Biagas and Kotake, 1983) and recent studies with human liver samples confirm this (Butler et al, 1989). The assay is currently being tested as a means to develop a urine caffeine metabolite test system to phenotype humans for levels of hepatic IA2. Such data on IA2 levels can be analyzed to determine if correlations exist with arylamine carcinogen exposure and cancer.

3. P450 IIC8. A P450, designated P450_{MP-3}, that is very similar in sequence to IIC9 has been isolated and its cDNA sequence has been determined (Ged et al, 1988). This cDNA has also been referred to as P450-1. IIC8 is capable of metabolizing hexobarbital (Ged et al, 1988), benzphetamine (Wrighton et al, 1987), retinol and retinoic acid (Leo et al, 1989). This enzyme, when analyzed by cDNA-directed expression, is also capable of catalyzing the methylhydroxylation of tolbutamide (Relling et al, 1989) although the enzyme purified from human liver has little tolbutamide hydroxylation activity (Ged et al, 1988). Purified IIC9 can catalyze tolbutamide hydroxylation in vitro (Ged et al, 1988; Wilkinson et al, 1989) and it is, therefore, unclear whether IIC8 or IIC9 is responsible for the polymorphic metabolism of tolbutamide (Scott and Poffenbarger, 1979). The role of IIC8 in drug polymorphism needs to be more carefully examined.

4. P450s IIIA3, IIIA4 and IIIA5. Some of the P450s in the *CYP3A* family are constitutively expressed in man. IIIA4, the most abundant IIIA protein, has been detected in most livers analyzed to date (Gonzalez et al, 1988; Waxman et al, 1988; Aoyama et al, 1989b). P450 IIIA3 (Molowa et al, 1986) is expressed to a much lesser extent than IIIA4 (Bork et al, 1989). The third enzyme, IIIA5, was detected in only about 10% to 20% of all human livers examined (Aoyama et al, 1989b). This latter P450, therefore, appears to be

polymorphically expressed in humans. IIIA4 is also variably expressed in man; up to 10-fold differences in levels of this enzyme have been detected in human liver microsomes by immunoblotting (Gonzalez et al, 1987; Waxman et al, 1988; Aoyama et al, 1989b).

P450s in the *CYP3A* subfamily metabolize a wide array of drug substrates including the tranquilizer midazolam, the immunosuppressant cyclosporine, the antibiotic erythromycin, the birth control steroid 17α -ethynylestradiol, the calcium channel blocker, nifedipine and a number of steroids such as cortisol and testosterone. The role of each IIIA P450 in metabolism of these drugs is currently under investigation using cDNA-directed expression.

One or more P450s in the IIIA (presumably IIIA4) subfamily are also involved in the activation of a number of carcinogens (Shimada et al, 1989), most notably aflatoxin B₁ (Shimada and Guengerich, 1989). Other carcinogens metabolized to mutagens by IIIA4 include aflatoxin b₁, sterigmatocystin, trans-7,8-dihydroxy-7,8-dihydrobenzo(a)pyrene, 6-aminochrysene, and tris-(2,3-dibromopropyl) phosphate.

In order to determine the role of IIIA4 in human carcinogenesis, assays must be developed to measure the enzymes in human populations known to be exposed to the above carcinogens. Nifedipine, a specific substrate for IIIA P450s (Gonzalez et al, 1987; Aoyama et al, 1989a), has been used to study human populations (Schellens et al, 1989). Endogenous metabolites of cortisol have also been suggested as monitors of IIIA4 metabolism in man (F.P. Guengerich, personal communication).

E. Flavin-Containing Monooxygenase

A flavin-containing monooxygenase is found in many tissues, which carries out the oxidation of a wide array of nitrogen and sulfur-containing compounds (Ziegler and Poulsen, 1978). Multiple forms of this enzyme are known to exist in liver and lung and these forms have distinct substrate specificities (Williams et al, 1985).

A polymorphism has been identified in a flavin-containing monooxygenase in man. Trimethylamine (TMA) and Trimethylamine *N*-oxide (TMAO) are compounds that occur naturally in marine fish. TMAO is formed from TMA by flavin-containing monooxygenase. A polymorphism in which TMA *N*-oxidation is impaired was discovered that is apparently due to a single gene inherited as an autosomal recessive trait affecting about 1% of the British population (AL-Waiz et al, 1987). This genetic defect is responsible for a condition referred to as "Fish-odor syndrome" in which individuals who are unable to metabolize TMAO exude an unpleasant smell (Humbert et al, 1970). The molecular basis of this defect has not been investigated due to the lack of cDNAs for the flavin-containing monooxygenase.

IV. OTHER DRUGS METABOLIZING ENZYMES

A. Carboxylesterases

These membrane-bound enzymes probably represent a group or superfamily of related proteins that carry out the hydrolysis of a large number of foreign compounds (Heymann, 1980; Hosokawa et al, 1987). The cDNAs for two rat carboxylesterases have been isolated (Long et al, 1988; Takagi et al, 1988). Little information exists on these enzymes in man, however.

B. Dihydrodiol Dehydrogenase

Dihydrodiol dehydrogenases are a little studied group of enzymes that metabolize many drugs and carcinogens. Multiple forms have been isolated from mouse (Bolcsak et al, 1983) but the multiplicity of these enzymes in rat and man is unknown. The enzyme is soluble and requires NADP^+ . Dihydrodiol dehydrogenase is capable of decreasing the mutagenicity of benzo(a)pyrene (Glatt et al, 1979) and benz(a)anthracene-8,9-diol 10,11-oxide (Glatt et al, 1982) in the Ames mutagenicity test. To date, cDNA clones for these enzymes have not been isolated and its presence and role in humans is still unknown.

C. DT Diaphorase (NAD(P)H:Quinone Reductase)

DT diaphorase has been proposed as an enzyme involved in protection against toxicity and carcinogenicity effects of chemicals (De Long et al, 1986; Prochaska and Talalay, 1988). This cytosolic enzyme has been extensively studied in rodents and it promotes two electron reduction of many types of quinones to hydroquinones. The number of forms of DT diaphorase is still unclear, although the cDNA sequence of a single form of the enzyme has been published (Robertson et al, 1986; Williams et al, 1986). Unfortunately little information exists on the human enzyme(s).

D. Epoxide Hydrolase

Two forms of epoxide hydrolase have been characterized to date, microsomal and cytosolic. These enzymes are structurally unrelated and have distinct substrate specificities. Since epoxide intermediates are frequently associated with DNA damage, epoxide hydrolases can be considered as protective enzymes. The human microsomal epoxide hydrolase cDNA has been cloned and sequenced (Skoda et al, 1988). High levels of the microsomal enzymes mRNA are generally found in human liver, although a few livers contain considerably less. Whether the hepatic content of the epoxide hydrolases influences susceptibility to chemical carcinogenesis is still unknown.

E. Glutathione Transferases

These enzymes catalyze the nucleophilic attack of the sulfur atom of glutathione on electrophilic groups in a second substrate. A gene superfamily of glutathione transferases exist. Three families, designated alpha, mu and pi have been described. These enzymes are expressed in multiple tissues and are found in most organisms (Mannervik and Danielson, 1988). The glutathione transferases are involved in detoxification of mutagens, carcinogens and other substances (Mantle et al, 1987). Many cDNAs, for different forms of glutathione transferase, have been cloned and sequenced from rodents and man. In man, three loci have been identified that code for these enzymes: the GST1, GST2 and GST3 loci code for the mu, alpha and pi enzymes, respectively. Recently, a mutation was found in man for a GST1 gene that encodes a leukocyte enzyme that conjugates trans-stilbene oxide (Seidegard et al, 1988). Lack of this enzyme has been correlated with susceptibility to lung cancer (Seidegard et al, 1986). A gene deletion was found in individuals that did not express both the trans-stilbene oxide conjugating enzyme and a GST1 mRNA in liver (Seidegard et al, 1988); however multiple GST1 genes exist and it is still unclear whether the deleted fragment corresponds to the appropriate gene. These provocative studies are the first to identify a mutated glutathione transferase gene.

F. UDP-Glucuronosyl Transferase

A superfamily of UDP-glucuronosyl transferases is known to exist in rat and man. These enzymes conjugate multiple foreign and endogenous substrates that contain hydroxyl groups to glucuronic acid. Multiple rat cDNAs have been cloned and sequenced (Mackenzie et al, 1984; Mackenzie, 1986). Recently, a human transferase cDNA was also cloned and sequenced (Harding et al, 1988). The existence of a human inherited defect in bilirubin conjugation (Crigler-Najjar syndrome) suggests that at least one form of transferase gene is deficient in man. More studies using cloned human transferase cDNAs should reveal whether other defective transferase genes exist.

G. Carboxymethyl-L-Cysteine Sulfoxidase

An enzyme that has not yet been purified, the carboxymethyl-L-cysteine S-oxidase is responsible for a high frequency polymorphism in man (Waring and Mitchell, 1989). Nearly a 100-fold difference was found between individuals in their ability to carry out this reaction and family studies suggested a genetic defect with allele frequencies of 0.17, 0.48 and 0.34 for homozygous EMs, heterozygous and homozygous PMs, respectively. This enzyme does not appear to play a significant role in carcinogen and mutagen activation but it may function in carcinogen protection by stimulating deactivation pathways.

V. ASSOCIATION OF DRUG METABOLIZING ENZYMES WITH CANCER SUSCEPTIBILITY

A. P450 IA1 and Cancer Susceptibility

The earliest P450 studies performed to answer the question "is expression of benzo(a)pyrene hydroxylase activity associated with human cancer susceptibility" were performed using isolated lymphocytes. In these experiments lymphocytes are taken from donors and incubated in culture with pokeweed mitogen and phytohemagglutinin. The cultures are then split and half of the cells were incubated with the IA1 inducer 3-methylcholanthrene or benz(a)anthracene. The cells are then processed and benzo(a)pyrene hydroxylase activities are measured using the highly sensitive fluorometric assay (Nebert and Gelboin, 1968). These experiments measured basal and fold-inducibility of the 3-hydroxymetabolite of benzo(a)pyrene. Verification that this activity reflects levels of IA1 mRNA (and protein) was obtained (Jaiswel et al, 1986). Kellerman et al (1973) suggested that IA1 inducibility was genetically determined and high inducibility was associated with lung cancer risk. The trimodal distribution of inducible activities observed by Kellerman et al (1973) has not been repeated by others (Paigen et al, 1977). The association with lung cancer has also not been observed in all studies (McLemore et al, 1978) but was confirmed by Kouri et al, (1982) who found a significant correlation between cigarette-induced bronchogenic carcinoma and benzo(a)pyrene hydroxylase inducibility using the ratio of P450 activity to NADPH-P450-reductase activity. Lymphocytes from lung cancer patients were found to be more inducible than the control group. Family studies were not performed to determine if the higher inducibility was due to genetic or environmental factors. Indeed, many factors affect the benzo(a)pyrene hydroxylase activities and inducibilities in lymphocytes including seasonal variation (Paigen et al, 1981), length of culture time (Hart et al, 1977), cell density, length of blood storage prior to experiment, source of mitogens, and variation between lots of fetal calf serum (Gurtoo et al, 1977). Under carefully controlled conditions, therefore, comparative studies can be carried out in a reproducible fashion.

Aryl hydrocarbon hydroxylase inducibility has also been studied in children with leukemia and their families. One study found no correlation of inducibility with leukemia and solid tumors (Levine et al, 1984). These investigators also found little evidence for a genetic component for aryl hydrocarbon hydroxylase. However, a more recent study, by analysis of acute childhood leukemia and by pedigree analysis, found evidence for a genetic component of increased inducibility with leukemia incidence (Yamashita et al, 1989).

In conclusion, it is still unclear whether aryl hydrocarbon hydroxylase inducibility is associated with cancer. Although intriguing linkages have been reported, further studies are required before firm conclusions can be drawn regarding this association.

B. IID1 Association With Cancer

Debrisoquine hydroxylase activity also has been correlated with cancer of the lung and bladder. In an extensive study carried out in London, a highly significant correlation was found between the metabolism of debrisoquine and lung cancer. Almost all lung cancer patients were extensive metabolizers of debrisoquine (Ayesh et al, 1984). In fact, these patients had a very high metabolic index as compared to the control population. Others, in a study carried out in Germany, found a distribution of PMs in lung cancer patients that was similar to the matched control population (Roots, et al, 1988). In patients under 50 years of age, however, none were PMs. The number of these patients was too small to conclude that there is any firm association of the metabolic phenotype with lung cancer. The reason for the association between IID1 activity and lung cancer in the London study is unclear since this enzyme is not known to metabolize carcinogens.

In another recent study, extensive debrisoquine metabolism was found to be associated with bladder cancer risk (Kaisary et al, 1987). Metabolism of mephenytoin and the acetylating phenotypes, however, were not risk factors. This association was only significant in patients with aggressive bladder cancer. Again, it is uncertain what role IID1 plays in the etiology of this cancer type.

Finally, the earlier studies of Ayesh et al (1984) were reevaluated to take into account the relationship of the debrisoquine metabolic phenotype with other risk factors such as occupational exposure to lung carcinogens and adjustment for age and smoking (Caporaso et al, 1989). It was found that the extensive metabolizer phenotype, when associated with occupational exposure to lung carcinogens, can result in a relative risk of up to 35.

Two possibilities could account for the association between the IID1 activity and cancer. First IID1 may be capable of activating an as yet unidentified environmental carcinogen, or a carcinogen in cigarette smoke. Individuals with high activities would be more prone to DNA damage and mutations. Second, it is also possible that an active *CYP2D6* allele may be linked to another cancer causing gene, for instance a second carcinogen metabolizing P450 or an active allele of an oncogene. Indeed, P450 genes are grouped into subfamilies that presumably are tandemly arrayed in close proximity on the chromosome. The *CYP2D6* gene is also known to be syntenic with the *SIS* oncogene on chromosome 22 (Gonzalez et al, 1988a).

VI. RECOMMENDATIONS FOR FUTURE STUDIES

A. Identification of the Human Enzymes Involved in Carcinogen Metabolism

The enzymes and genes for human P450s and transferases must be isolated from the appropriate tissues and characterized. Their substrate specificities must also be determined. Expression of these enzymes should be analyzed in a large number of individuals or tissue samples to determine if they are polymorphically expressed. For example novel liver (Aoyama et al, 1989b; Yamano et al, 1989) and lung (Nhamburo et al, 1989) P450 cDNAs have been identified and expressed into active enzymes. The expression of these P450s has also been analyzed in multiple human liver and lung tissues taken from kidney donors.

B. Development of Human Drug-Metabolizing Enzyme-Based Carcinogen Testing Systems

The mechanisms of species differences in drug metabolism have unfolded over the last several years. These differences call attention to problems associated with using rodents to test the toxicity, mutagenicity and carcinogenicity of compounds such as drugs under development and industrial pollutants. Through the use of cloned human genes, cell lines and vectors can be developed that can be used as testing systems (Aoyama et al, 1989a; Crespi et al, 1989; Davies et al, 1989).

C. Development and Refinement of Methods to Detect Levels of Expression of P450s and Alter Drug Metabolizing Enzymes

1. In vivo metabolic methods to identify polymorphism in drug and carcinogen metabolism. Currently methods exist to phenotype individuals for the presence or absence of a particular P450. These methods involve the administration of drugs at subtherapeutic doses and the quantitation of P450-mediated metabolites. Problems associated with some of these measurements have been discussed by Wilkinson et al (1989). For example, simultaneous administration of other drugs or of dietary substances, both of which can compete for the P450 active site, can affect in vivo measurements. The P450s that currently can be measured are those active in drug metabolism but inactive in the metabolism of carcinogens. Therefore, non-hazardous chemical probes should be developed for P450s known to be involved in carcinogen activation. For example, caffeine is being tested as a probe to simultaneously measure both acetylation (see Weber in this volume) and IA2-mediated metabolic capacity. Warfarin may also turn out to be a useful probe to phenotype other P450s.

2. Lymphocyte DNA-based methods to probe for mutant genes coding for drug metabolizing enzymes. The ideal method to analyze for mutant genes is to examine lymphocyte DNA. The DNA can be obtained easily and its analysis is not subject to the problems encountered in *in vivo* measurements, as discussed above. In addition, direct gene analysis will allow the identification of heterozygotes, a virtual impossibility with *in vivo* methods. A preliminary report has been published in which restriction fragment length polymorphisms (RFLPs) have been used to identify mutant *CYP2D6* (IID1) genes (Skoda et al, 1988). Unfortunately, only about 70% of the mutant alleles currently can be identified using this procedure. The most likely method that will allow accurate determination of mutant alleles will be polymerase chain reaction-based (PCR) procedures (Saiki et al, 1988). However, in order to use PCR, the complete sequences of the P450 genes must be obtained and mutant alleles also must be directly identified. This requires an extensive effort but should be very valuable in the future identification of genes involved in cancer susceptibility.

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CHAPTER 2

Acetylation

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I. HEREDITARY METABOLIC POLYMORPHISMS AS MODULATORS OF HUMAN CANCER

A. The Acetylation Polymorphism and Metabolic Activation of Carcinogenic Aromatic Amines

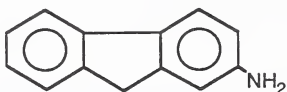
Person-to-person differences in the metabolism of amines and hydrazines, whether they are drugs used in medical therapy, carcinogens in the workplace or elsewhere in the environment, or endogenous substances such as the neurotransmitter, serotonin, are attributable in part to the polymorphism in the acetylator genes. Consequently, the therapeutic, pharmacologic and toxicologic responses of individuals to these chemicals may also differ remarkably.

The polymorphism in the acetylator genes, recognized more than three decades ago during investigations of the antituberculous drug, isoniazid, is an autosomal, monogenic, Mendelian trait. Genetically, individuals are either "slow" acetylators, homozygous (rr) for a slow acetylator gene, or "rapid" acetylators heterozygous (Rr) or homozygous (RR) for a rapid acetylator gene. Though the acetylating capacity of the individual is remarkably stable, it may vary by 10-fold or more from individual to individual. The chromosomal locus of the human N-acetyltransferase gene is yet to be determined, but linkage studies in mice indicate it is located on mouse chromosome 8, approximately 12 centimorgans from the Esterase-1 locus (Mattano et al, 1988).

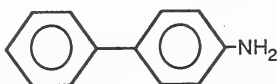
Enzymologically, rapid and slow acetylator phenotypes are characterized by qualitatively distinct isozymic variants of the acetylating enzymes (N-acetyltransferases) of cytosols of liver, intestinal mucosa and certain other tissues. Differences in the activity and affinity of the rapid and slow acetylator isozymes for aromatic amine substrates appear to account for the difference in the in vivo acetylating capacity of the rapid and slow acetylator phenotypes. Human studies, augmented by studies of several animal species which have a similar genetic acetylation polymorphism, indicate that the polymorphic N-acetyltransferase of liver is a monomeric protein whose molecular weight, depending upon the species, is 31,500–33,000 kilodaltons. The rapid and slow

acetylator enzymes of each species appear to be isozymes of a nearly identical acetylating enzyme, but there are species differences in the primary structure of the parent enzymes (Weber et al, 1989).

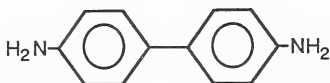
Human metabolic studies of arylamine carcinogens. The effect of heredity on the metabolic activation of arylamine carcinogens (Fig. 1) by human tissues has been studied only for the past ten years or so. Initial studies of fresh



2-Aminofluorene



4-Aminobiphenyl



Benzidine

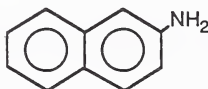
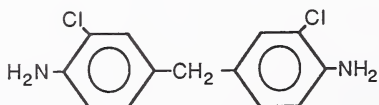
 β - Naphthylamine4,4'-Methylene-bis-
(2-Chloroaniline)

Fig. 1. Polymorphically acetylated arylamine carcinogens.

human liver biopsies showed that the N-acetylation of the carcinogens benzidine, beta-naphthylamine, 2-aminofluorene and methylene-bis-(2-chloroaniline), an early step in the metabolic activation of these chemicals, was differentially catalyzed by rapid and slow acetylators (Glowinski et al, 1978). This study suggested a possible relationship between hereditary acetylator status and cancer susceptibility. More recent studies, focused on the subsequent steps in the conversion of the hydroxylamine and hydroxamic acid derivatives of 2-aminofluorene to DNA-bound adducts in human liver preparations, have led to similar conclusions. Although the original genetic and enzymologic studies of the acetylation polymorphism concentrated mainly on the liver, it is now appreciated that expressions of this trait in extrahepatic tissues, such as human colonic tissue (Flammang et al, 1987; Kirlin et al, 1989) and human urinary bladder (Hein, 1988a), may play an important role in the etiology of arylamine-induced cancer in these tissues.

For all well-studied arylamine carcinogens, adducts of the carcinogen to DNA have been identified (Beland and Kadlubar, 1985). Several important generalizations about the activation process and the structures of carcinogen-DNA adducts have emerged from investigations of aromatic amine mutagenesis and carcinogenesis and its genetic control:

Arylamine carcinogen-DNA adducts are generated either by reactions with N-hydroxylamine or N-hydroxyarylacetamide (arylhydroxamic acid) metabolites of the amine. Precursors of the ultimate carcinogens are produced enzymatically through N-oxidation of the amines by cytochromes P-450, flavin-containing monooxygenases, or peroxidases (Fig. 2). Further activation of the arylhydroxamic acids involves either deacetylation to the hydroxylamine, N,O-acyltransfer to the N-acetoxyarylhydroxylamine, or conjugation with activated sulfate by sulfotransferase to the N-sulfoxyacetamide. N,O-acyltransfer and O-acetyl transfer both generate nonacetylated DNA adducts, whereas sulfotransfer generates acetylated adducts.

Mechanisms for AcCoA-dependent activation of the N-hydroxylamines involve either direct O-acetylation by AcCoA-dependent O-acetyltransferase (OAT), or N,O-acetyltransfer via N,O-arylhydroxamic acid acyltransferase (AHAT) (Flammang and Kadlubar, 1986). Both pathways lead to the reactive N-acetoxyarylamine product (Fig. 2), but substrates such as N-hydroxy-2-aminofluorene, that theoretically could be activated by either of these mechanisms, are activated preferentially by direct O-acetylation rather than N,O-acetyltransfer. In mouse tissues, the evidence suggests that N- and O-acetyltransferase activities are catalyzed by a common enzyme (Flammang and Kadlubar, 1986; Mattano et al, 1989). By contrast, the relationships between N,O-acyltransferase and both the N- and the O-acetyltransferase activities in human tissues are less well understood.

Acetylated and non-acetylated adducts are formed in the target and non-target tissues. The majority of the adducts form at the C-8 or the N-2

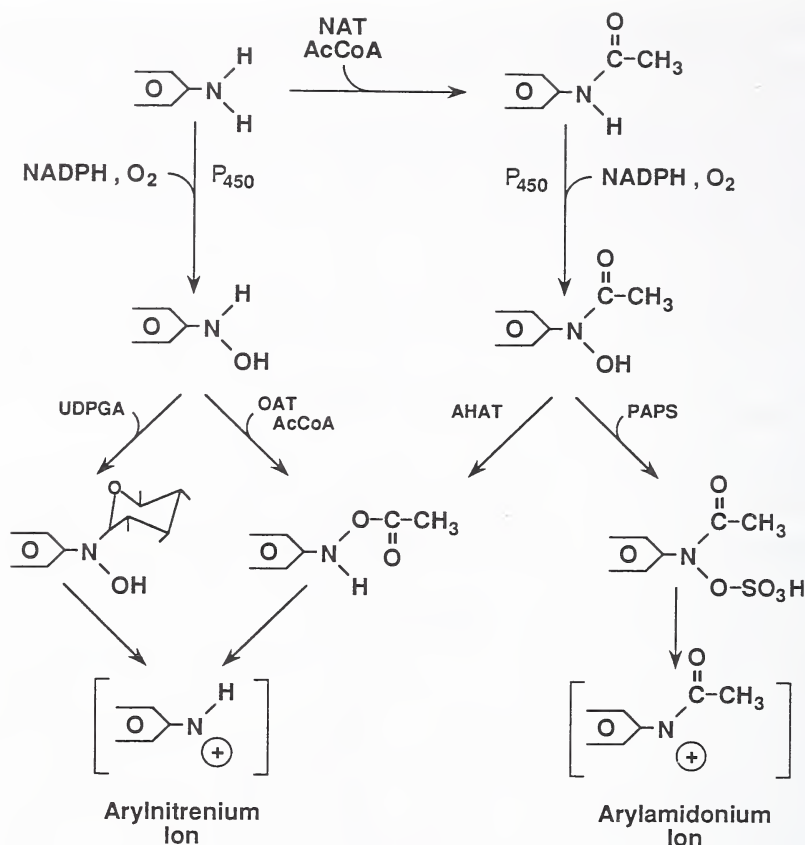


Fig. 2. Parallel pathways proposed for the metabolic activation of arylamines to carcinogenic metabolites. R-NH_2 = arylamine carcinogen; R-NH-COCH_3 = N-acetylated arylamine; R-NHOH = hydroxyarylamine; $\text{R-N(OH)(COCH}_3\text{)}$ = arylamine hydroxamic acid; R-N(OH)(sugar) = N-glucuronide of the hydroxyarylamine; $\text{R-NH(OCOCH}_3\text{)}$ = O-acetylated arylamine; $\text{R-N(COCH}_3\text{)(SO}_3\text{H)}$ = acetylated sulfated arylamine; P_{450} = microsomal cytochrome oxidizing enzyme; NAT = N-acetyltransferase enzyme; OAT = O-acetyltransferase enzyme; AHAT = arylhydroxamic acid acyltransferase enzyme; AcCoA , NADPH , O_2 , UDPGA and PAPS are enzyme cofactors.

positions of guanine, but the unacetylated C-8 adduct predominates (Neumann, 1986). The presence of these adducts is correlated in short-term tests with mutagenicity and carcinogenicity.

The persistence of different DNA-carcinogen adducts differs from adduct to adduct, and their effects are unevenly distributed in tissues. The extent of the heterogeneity appears to be explained partly by different concentrations of the reactive metabolites that are generated within tissues because of pharma-

cokinetic differences, and differences in the capacity of tissues for metabolic activation (Kriek et al, 1984). Variability in DNA base composition and in the relative accessibility of different DNA regions may also influence the distribution of adducts (Lasko et al, 1988) and the effects of the adducts (Vousden et al, 1986; Pfohl-Leszowicz et al, 1988). Differences in DNA repairability may also contribute.

For aromatic amine carcinogens in rapid and slow acetylators, differences in tumorigenesis appear to be related to differences in the concentrations of reactive metabolites in their tissues. Moreover, these differences are probably secondary to both the pharmacokinetic differences in disposition of these amines and to differences in enzymatic capacity for metabolic activation imposed by the acetylator genes as well as other genes of the individual (Levy and Weber, 1989).

Cancer Epidemiology in Rapid and Slow Acetylators

A statistical association between human acetylator status and cancers of the urinary bladder, colon, breast, larynx and stomach has been reported.

Urinary bladder cancer: First reports of urinary bladder tumors appeared in Germany just before the turn of the century (Rehn, 1895). Though at first this attracted little attention, during the next 30 years, enough epidemiologic and experimental evidence had been gathered to call attention to industrial bladder cancer among naphthylamine and benzidine workers (Parkes and Evans, 1984). However, Case et al (1954) were the first to establish that the risk of contracting bladder cancer was approximately 30 times greater for exposed chemical workers than for the general population. Since then, occupational exposure to aromatic amines has been widely regarded as the major cause of this disorder.

There are now at least a dozen studies reporting the association of acetylator phenotype to urinary bladder cancer (reviewed in Weber, 1987; Hein, 1988b, and updated here). A significant excess of slow acetylators is affected (Table 1). The difference is greatest in the slowest of the slow acetylators (Cartwright et al, 1982; Mommsen and Aagard, 1986; Bicho et al, 1988), among smokers as compared to nonsmokers (Mommsen and Aagard, 1986), and among workers at highest risk of exposure to aromatic amines (Table 1). Additionally, a significant association of tumor aggressiveness with the slow acetylator phenotype has been observed in two studies (Cartwright et al, 1982; Mommsen and Aagard, 1986), but not in a third (Hanssen et al, 1985).

The strongest association of slow acetylator phenotype to urinary bladder cancer occurs in persons exposed occupationally to aromatic amines such as benzidine. Cartwright et al (1982) described a group of 23 men with bladder cancer, all of whom had been employed in the chemical dye industry. Twenty-two of 23 had transitional cell tumors and were slow acetylators

TABLE 1. The Relative Risk of Human Cancer in the Rapid (R) and Slow (S) Acetylator Phenotypes

Cancer	Number of Studies	Relative Risk	Chi-Square
Bladder cancer			
All studies	12	S vs R = 1.33	10.01 (p < 0.01)
High risk of exposure	3	S vs R = 1.70	7.82 (p < 0.01)
Colorectal cancer	2	R vs S = 3.03	11.90 (p < 0.001)
Breast cancer	3	R vs S = 1.20	1.49 (p > 0.10)

Relative risks computed by Haldane's modification (1956) of Woolf's method (1955). Summarized from Weber (1987).

including 12 who had carcinoma in situ. Occupationally exposed bladder cancer patients have been reported by two other investigators (Ladero et al, 1985; Lower in Weber et al, 1983). Table 1 indicates a relative mean excess of slow to rapid acetylators of 1.33 ($\chi^2 = 10.01$, $p < 0.01$) for all studies, but this is largely due to the contribution of persons exposed at work ($\chi^2 = 7.82$, $p < 0.01$).

Cigarette smoke is a recognized cause of bladder cancer (Parkes and Evans, 1984), but there is little, if any, relationship to acetylator phenotype (Mommensen and Aagard, 1986; Cartwright et al, 1982). These observations are noteworthy because cigarette smoking is an etiologic factor confined to the nonaggressive, papular form of the disease and not to carcinoma in situ, aggressive form (Cartwright and Barham-Hall, unpublished). Cigarettes contain such a minute dose of aromatic amines, such as beta-naphthylamine, that they may be detoxified as well by slow as by rapid acetylators. At higher doses, as can occur in an industrial setting, the effects of the deficiency become evident.

Colorectal cancer: Two studies indicate that rapid acetylators may be more susceptible than slow acetylators to colorectal cancer (Lang et al, 1986; Ilett et al, 1987). Flammang and colleagues (1987) have found high levels of acetyltransferase activity in human colonic mucosa. They have found, further, that the mucosa itself catalyzes the O-acetylation of the N-hydroxy metabolites to DNA-reactive metabolites (Flammang et al, 1985; Flammang and Kadlubar, 1986) that could initiate large bowel cancer. Other evidence indicates that various heterocyclic arylamines derived from cooked fish and meat, and from pyrolysis of proteins and amino acids can be metabolically activated to genotoxic forms capable of mutagenesis and carcinogenesis (Sugimura, 1988). Thus, there is reason to expect that the genesis of some colorectal cancers may be related to aromatic amine carcinogens and that rapid acetylator genes may predispose individuals to this disorder.

Breast cancer: An association between acetylator phenotype and malignant breast disease in women has been reported by Bulovskaya et al (1978) and by

Cartwright (1984). Statistical analysis of both data sets shows a significant excess of 2.05 rapid to slow acetylators ($\chi^2 = 8.99$, $p < 0.01$). Recently others (Philip et al, 1987; Ladero et al, 1987) failed to confirm this observation for women with malignant breast disease. However, a significant trend associating rapid acetylators with more advanced disease is found, and a slight, nonsignificant excess of rapid acetylators is found in patients with benign breast disease. Further, no relationship is found between estrogen or progesterone receptors, or age, and the acetylator phenotype (Philip et al, 1987).

The evidence thus does not support an obvious association between acetylator status and breast cancer, but the relationship in the subset of women who use hair dyes has not been examined and there may be a case for this. Shore et al (1979) found a statistically significant association between permanent hair dye use and breast cancer in women 50 years old or older after a latency of 10 or more years, though none was found for younger women with a high natural risk of this disorder. p-Phenylenediamine, a common constituent of permanent (oxidative) hair dyes, becomes strongly mutagenic to *Salmonella typhimurium* TA 1538 when it is mixed with hydrogen peroxide just before use (Searle et al 1975), and carcinogenic to the mammary gland of female rats (Rojanapo et al, 1986a,b). Additionally, the mechanism of induction of tumors by amines of this type is related to the N,O-acyltransferase content of the mammary gland (Malejka-Giganti et al, 1973, 1975; King and Allaben, 1978). Shore's study is intriguing but it needs validation because it is retrospective and uncertainties arise from the small numbers of participating subjects. In the face of incomplete and conflicting epidemiologic evidence (Wilson, 1985), it seems unwarranted to set aside the possible role of acetylator phenotype in breast cancer in hair dye users.

Cancer of the larynx and stomach: One recent study reports the association of the slow acetylator phenotype with laryngeal cancer in a Polish population (Drozd et al, 1987). In that study 83.6% (107/128) of patients with laryngeal cancer were slow acetylators compared to 60.3% (64/106) of noncancerous control subjects ($\chi^2 = 16.0$, $p < 0.001$). Both laryngeal cancer patients and controls consisted mainly of smokers. Analysis of the data shows a relative risk ratio of slow/rapid acetylators of 1.88 ($\chi^2 = 29$, $p < 0.0001$).

A preliminary report of a German study (Drakoulis et al, 1988) reveals an excess of slow acetylators in both histologic types (intestinal and diffuse) of gastric cancer, but no further information about the study is available.

Detailed biochemical assessment of the activation of carcinogenic arylamines, summarized in Figure 2, suggests a rationale for the statistical association of bladder cancer with the slow acetylator phenotype on one hand, and for the putative association of colorectal cancer with the rapid acetylator phenotype on the other. Activation in these tissues appears to involve separate but interrelated parallel pathways. Arylamines and N-hydroxyarylamines can

be transported as their N-glucuronide conjugates to the bladder and colon, where the mildly acidic urine of the bladder or the glucuronidases of the gut can regenerate the amines or N-hydroxylamine. Because of their relatively lower hepatic acetylating capacity, the bladders of slow acetylators, especially the slowest of the slow acetylators, would be exposed to greater amounts of the arylamine and the N-hydroxylamine, and hence to greater risk of cancer than the bladder of rapid acetylators. In contrast, the activation of N-hydroxylarylamines via O-acetylation in colorectal tissue (Flammang et al, 1985; Flammang and Kadlubar, 1986), and preliminary reports documenting its coregulation with polymorphic arylamine N-acetylation in human subjects (Flammang et al, 1987) may explain the excess of rapid acetylators in colorectal cancer patients.

Biomonitoring Human Exposure to Aromatic Amines

Only a few attempts to assess the importance of the acetylator status of individuals to toxicity from aromatic amines by conventional monitoring techniques have been reported. Lewalter and Korallus (1985) found in persons acutely exposed in a German chemical factory to aniline derivatives that the capacity for acetylation is inversely related to the concentrations of methemoglobin and hemoglobin-aniline conjugates found in blood. Even high accidental exposures lead only to relatively low, or undetectable levels of hemoglobin-aniline conjugates in rapid acetylators. In contrast, slow acetylators exhibit formation of methemoglobin and hemoglobin conjugates, and the conjugates persist throughout the lifetime of the red cell.

Dewan et al (1986) found that workers in a benzidine factory absorbed sufficient amounts of benzidine through their skin to be easily measured in the urine. Slow acetylators attain significantly higher blood benzidine concentrations and eliminate it more slowly in urine than rapid acetylators. An earlier study of persons exposed occupationally to another aromatic amine carcinogen, methylene-bis(o-chloroaniline, MOCA), reported persons divisible into groups of "nonexcretors," "intermediate excretors" and "excretors" of MOCA (Linch et al, 1971). The investigators did not suggest that "nonexcretors" may have been rapid acetylators and "excretors" may have been slow acetylators, though this seems quite possible.

The traditional biomonitoring techniques can provide valuable information on patterns of metabolites accompanying exposure, but they are not designed for determining carcinogenic dosimetry or preclinical response that are essential to risk assessment. Early attempts to use methemoglobinemia to gain insight into the toxicity of aniline (Druckrey, 1950) and of azodyes (Neish, 1959) failed, but Neish may have been the first to suggest the measurement of carcinogenic potency by analyzing hemoglobin or its fate in red cells. In the meantime, the Millers (1947) had demonstrated the covalent binding of an

analog of the arylamine carcinogen, 4-aminobenzene, to hepatic protein, and clarified the significance of that observation by using another aromatic amine derivative, 2-acetylaminofluorene, to demonstrate that biotransformation to reactive metabolite(s) is a prerequisite for the macromolecular damage caused by many xenobiotics (Cramer et al, 1960). As a result of an intensive study in many laboratories during the next two decades, the concept of metabolic activation is now generally accepted, and investigators have reached a consensus on the reactions implicated in the metabolic activation of carcinogenic arylamines. Also the ultimate carcinogen(s) have been identified for a number of arylamines (reviewed in Weber, 1987; Hein, 1988b).

Consequently, investigators of risk assessment have begun to focus on DNA and protein adducts to improve biologic dosimetry. Data on the relationship of adduct formation to either gene mutation/initiation or cancer are as yet largely limited to experimental systems; but in instances where the critical adduct(s) have been measured, a good correlation between chemical adduct formation and carcinogenic potency exists (Perera, 1987, 1988).

At the present stage of knowledge, the utility of DNA and protein adducts as quantitative predictors of risk may be best evaluated by parallel prospective studies of experimental animals and humans exposed to environmental carcinogens. Until recently, appropriate techniques and experimental animal models to investigate the relationship of the role of the human acetylation polymorphism to adduct formation have been unavailable. However, recent advances in highly specific and sensitive techniques for measuring adduct formation with arylamines (Randerath et al, 1981, Gupta et al, 1982; Levy and Weber, 1988), and the recent development of congenic acetylators inbred mouse strains (Mattano et al, 1988) has permitted the performance of metabolic studies (Hein et al, 1988) in conjunction with studies of adduct formation (Levy and Weber, 1989). Studies of this type should aid in assessing this relationship more rigorously.

New developments in other areas should also aid the collection of human epidemiologic information on the importance of the human acetylator polymorphism in arylamine-induced cancer. For example, previous methods provide a means of discriminating rapid and slow acetylator phenotypes, but the caffeine test, as recently revised, (discussed further below) surpasses other procedures by discriminating homozygous and heterozygous rapid acetylators from each other and from slow acetylators (Tang et al, 1987; Kilbane et al, 1990). Moreover, several novel approaches to biomonitoring the dosimetry of aromatic amines in humans, some of which are promising for population study, are under study. Examples of these include the measurement of hemoglobin-carcinogen adducts of 4-aminobiphenyl and other arylamines in human subjects (Neumann, 1984; Bryant et al, 1987), the use of human peripheral blood lymphocytes to measure amine carcinogen-DNA binding

capacity (Gupta et al, 1988), in vivo dosimetry by measurement of cysteine adducts of hemoglobin (Green et al, 1984) or serum albumin (Skipper et al, 1985), and the immunochemical quantitation of 4-aminobiphenyl-DNA adducts from human urinary bladder (Roberts et al, 1988).

II. LABORATORY TECHNIQUES FOR IDENTIFYING HUMAN METABOLIC PHENOTYPES

A. Human Acetylator Phenotype Determination

Human beings are divisible into rapid and slow acetylator phenotypes. The acetylator phenotype is expressed early in life, probably during infancy, and is remarkably stable throughout the the life of the individual. Any of several drugs and analytical procedures can be used to classify healthy adults as rapid and slow acetylators, but caution is necessary in interpreting this information in altered physiologic states and in the presence of certain diseases and environmental chemicals. For a more comprehensive discussion of the determination of the human acetylator phenotype and genotype see Weber (1987).

Pharmacologic Procedures

At least 30 pharmacologic procedures for determining the human acetylator phenotype that use seven different drugs and numerous analytical techniques in various combinations have been published. The drugs used most frequently are isoniazid, sulfamethazine, sulfapyridine, dapsons and caffeine. Isoniazid was the first and only drug used for many years for this purpose (Evans et al, 1960; Evans, 1969). Eidus et al (1973) introduced a simple, noninvasive procedure that clearly differentiates rapid and slow acetylators from estimates of the acetylisoniazid/isoniazid ratio in urine six to eight hours after oral ingestion of isoniazid. This method is automated (Varughese et al, 1974) and modified further for analysis of urine collected 24 hours after ingestion of a slow release preparation of isoniazid (Ellard et al, 1973).

Sulfamethazine (sulphadimidine) frequently has been used to determine the human acetylator phenotype because its acetylated derivative is very stable and the chemical analysis of sulfamethazine is rapidly and relatively easily performed (Evans, 1969; Rao et al, 1970). Rapid and slow acetylators are clearly differentiated by determination of the ratio of acetyl sulfamethazine/sulfamethazine in venous blood or urine 6 hr after sulfamethazine ingestion. Discrimination in blood surpasses that in urine because measurements of the ratio in urine are more sensitive to variations in renal function, urine pH, and urine flow rates than in blood.

Sulfamethazine approved for human use is becoming more difficult to obtain, and this has greatly reduced the popularity of this method; but sulfapyridine, an approved drug that is readily available, is equivalent to

sulfamethazine for determination of the human acetylator phenotype (Schroder and Evans, 1972). A method of acetylator phenotype determination with sulfapyridine by HPLC has been reported by Vree et al (1980).

Yesair and colleagues (Callahan et al, 1981) found acetylation to be implicated in the metabolism of caffeine in human subjects, and Grant and co-workers (1983a,b, 1984) applied this information advantageously to develop a noninvasive method of acetylator phenotype determination. Subjects ingest caffeine either in a single dose (300 mg) or in coffee, tea or cola soft drinks, and urine collected two to six hours afterward is analyzed by HPLC. Caffeine is not acetylated directly, as are the other drugs used for acetylator phenotype determination, but first undergoes oxidative ring cleavage mediated by microsomal monooxygenases, and the AFMU (5-acetyl-6-formylamino-3-methyluracil) metabolite formed is subsequently polymorphically acetylated. The ratio of AFMU/1X where 1X stands for 1-methyl xanthine, is bimodally distributed. The modal frequencies of AFMU/1X correspond closely to those obtained with sulfamethazine and are used to differentiate the rapid and slow acetylator phenotypes.

Acetylator genotype determination: A method of determining the acetylator genotype is of interest because it would afford additional opportunities to test the relationship of acetylator status to arylamine-induced cancer.

An effect of the acetylator gene in the heterozygote is evident in vitro in rapid and slow acetylator rabbit tissues. It is evident both in vitro and in vivo in other animal species that express hereditary acetylation polymorphisms such as the mouse and hamster (reviewed in Weber, 1987). An effect of heterozygosity has also been noted in human subjects, but it is not large enough to enable us to differentiate with confidence homozygous (RR) from heterozygous (Rr) rapid acetylators with the pharmacologic procedures already mentioned, despite occasional claims to the contrary (Chapron et al, 1980; Lee and Lee, 1982).

Sunahara et al (1961, 1963) and Dufour et al (1964) first reported trimodal distributions of isoniazid acetylation capacity in which observed frequencies of all three acetylator genotypes agreed with expected values. The microbiologic procedures used in these studies have fallen into disuse because they do not differentiate isoniazid from its hydrazones, unstable metabolites that have antituberculous activity, and because they require several days to perform.

In addition to finding the caffeine test useful to differentiate rapid and slow acetylators, Grant et al (1984) observed a trimodal distribution of the AFMU/1X ratio, but the distribution of individuals into homozygous and heterozygous genotypes does not fit the distribution expected from the Hardy-Weinberg law. AFMU is relatively unstable in mildly acid conditions such as occur in human urine, spontaneously undergoing deformylation to the stable metabolite, AAMU (5-acetyl-6-amino-3-methyluracil). By using the alterna-

tive metabolic ratio $AAMU/(AAMU + 1X + 1U)$, where 1U is 1-methyluric acid, separation of homozygous and heterozygous rapid acetylators now seems possible (Tang et al, 1987). Further modification of Tang's method and definitive pedigree analysis in 15 families (75 subjects) yields a trimodal distribution in agreement with Mendelian segregation (Kilbane et al, 1990). This provides additional evidence that the human acetylator genotype can now be reliably determined.

Effects of Altered Physiology, Disease and Environmental Factors on the Determination of Acetylator Status

The amount and quality of the polymorphic acetyltransferases are the key elements in affixing the acetylator capacity of the individual. Determination of the acetylator phenotype or genotype by pharmacologic procedures depends on the concentration of the test drug and/or its acetylated metabolites attained in blood or urine under standardized conditions. The rate and extent of the drug's absorption, distribution, metabolism by pathways other than acetylation, and its excretion may influence these concentrations. Each of the latter processes of drug disposition is subject to the influence of physiologic, pathologic and environmental factors.

Human studies suggest that genes other than the acetylator genes can also influence acetylation (White and Evans, 1968). More definitive support for this conclusion comes from several studies in inbred (Glowinski and Weber, 1982) and congenic acetylator mouse strains that express an hereditary acetylation polymorphism (Hein et al, 1988; Levy and Weber, 1989). Further investigation is needed to specify the genes that are involved.

Several physiologic and pathophysiologic factors are postulated to have an influence on the determination of the human acetylator status as follows:

Body weight: Several studies draw attention to the importance of body weight in the determination of acetylator phenotype in individuals (reviewed in Weber, 1987). Thus, high-weight subjects tend to have higher plasma isoniazid concentrations than low-weight subjects, and the tendency is greater for the slow phenotype. This could lead to misclassification of low-weight subjects in some instances (Evans et al, 1961). Moreover, different drugs may yield dissimilar results (cf. Evans et al, 1961; Chapron et al, 1982).

Age, gender and other physiologic factors: A bimodal distribution of isoniazid concentrations in children suggests that the acetylation polymorphism is expressed as early as one year of age, and possibly earlier (Mount et al, 1961). Greater rates of isoniazid elimination occur in infants and younger children compared to older children and adults (Houin and Tillement, 1980; Bouvert et al, 1983; Paire et al, 1984), but this can probably be explained by the relatively greater mass of liver in proportion to the total body weight during infancy and childhood (Lupasco et al, 1965). Several studies of the

effect of old age on the acetylator phenotype have led to divergent results (Farah et al, 1977; Advenir et al, 1980; Gachalyi et al, 1984, 1985; Paulsen and Nilsson, 1985; Pontiroli et al, 1985; Kergueris et al, 1986), but none convincingly demonstrates an age-related change in the acetylator phenotype beyond the first year after birth.

The effects of *body position and activity* may also affect drug disposition in persons being phenotyped. Isoniazid half-lives are prolonged about 20% by changing from a recumbent position to walking (Levi et al, 1968), whereas intense physical exercise raises both acetylated and nonacetylated sulfamethazine concentrations while the degree of acetylation is unaffected (Ylitalo and Hinkka, 1985). Dissimilar effects occur with different drugs.

Renal disease: No simple generalization can be made about the reliability of the acetylator phenotype determination of patients with impaired renal function using the pharmacologic procedures mentioned above. Some evaluations of patients with moderately reduced renal function conclude that such procedures can give a clear separation of rapid and slow acetylators (Talseth and Landmark, 1977; Hall, 1981; Koopmans et al, 1984) while others disagree (Molin et al, 1977; Lima and Jusko, 1978). The results may also differ for different test drugs, and for different procedures that use the same test drug (Hansson and Sandberg, 1973; Molin et al, 1977; Koopmans et al, 1984). The results of phenotype determinations must be interpreted with reservation in persons in whom the elimination of either the parent drug or its acetylated metabolite is hindered. For persons with severe renal impairment, the acetylator phenotype can only be consistently defined from an estimate of metabolic clearance rates (Fine and Summer, 1975). Measuring the metabolic clearance rate involves the determination of total renal and metabolic clearance of unacetylated and acetylated test drug(s). Such measurements are time consuming and not readily adapted to the collection of epidemiologic data on more than a few persons.

Liver disease: Only one study of the effect of liver disease on the determination of the human acetylator phenotype has been reported (Levi et al, 1968). In persons with acute and chronic liver disease the half-life of isoniazid is prolonged and loses the bimodal character typical of healthy persons. This prolongation correlates with the elevation of serum bilirubin and reverses as the patient improves. Even though the average degree of prolongation of the half-life is statistically significant, it is quantitatively less important than the intrinsic genetic effect on acetylation.

Diet, drugs and other environmental substances: A comprehensive account of the influence of environmental agents on the outcome of acetylator phenotype determination cannot be made because they are so diverse, and so few of them have been studied adequately. A few studies that examine the influence of specific dietary components, certain drugs and other environmental sub-

stances are noted to illustrate the effects observed and their potential importance. For example, high carbohydrate meals reduce the absorption of isoniazid, perhaps by forming unabsorbable condensation products with sugars (Mannisto et al, 1982); antacids and laxatives have a similar effect (Hurwitz and Schlozman, 1974). In contrast, insulin has the opposite effect, resulting in decreased concentrations of the drug in kidneys and brain and increased concentrations in the lung, skin and liver (Danyasz and Wisniewski, 1970). Isoniazid elimination rates are significantly enhanced by glucose ingestion (Thom et al, 1981) and decreased by starvation (Buchanan et al, 1979). However, a comparison between undernourished and well-nourished subjects shows no effect on the acetylator status as determined with sulfamethazine (Shastri, 1982). Acute ingestion of ethyl alcohol may increase drug acetylation so that misclassification of some slow acetylators as rapid acetylators may occur (Olsen and Morland, 1982). Glucocorticoids such as prednisolone cause significant decreases in plasma isoniazid concentrations in both rapid and slow acetylators, but the effect is more pronounced in the slow acetylators (Sarma et al, 1980). Animal studies suggest the effect may be due to liver cell hypertrophy, resulting in greater N-acetyltransferase activity per cell (Reeves et al, 1988). The effect on the determination of the human acetylator phenotype has not been investigated.

The Need for Improved Methods of Acetylator Phenotype Determination

Most of the pharmacologic procedures are reliable for differentiating rapid (RR, Rr) from slow (rr) acetylator phenotypes, but many also have disadvantages that have hampered the collection of those epidemiologic data that can relate the hereditary acetylation polymorphism to human diseases. Invasive procedures that require the administration of a test drug such as isoniazid, sulfamethazine and so on are impractical for use in sick or elderly patients and in newborn infants and young children, or in persons remote from medical facilities. The question of drug idiosyncrasy (eg, to sulfonamides), drug sensitivity (such as that associated with G6PD deficiency), or other incompatibilities that may accompany intake of other test drugs must be considered. In other circumstances, ethical constraints may be paramount (Lewalter and Korallus, 1985). Patients with impaired renal function may be difficult to classify (Fine and Summer, 1975; Lima and Jusko, 1978).

Because caffeine is so widely used as a food additive, it is more acceptable than the other test drugs for acetylator phenotype determination of children and adults. This and its utility in the determination of the acetylator genotype, as well as the phenotype, suggest that caffeine is the pharmacologic agent of choice for the collection of data to assess the significance of the human hereditary acetylator polymorphism as an etiologic factor in cancer. Despite

the advantages of caffeine, the techniques of molecular biology ultimately hold much greater promise for this purpose. The identification and characterization of gene differences at the DNA level have been made possible through differential hybridization of oligonucleotide probes designed to span the region of the genome where the genetic difference of interest lies. Enrichment of this region of DNA through the development, subsequent improvement and automation of the technique of the polymerase chain reaction has greatly facilitated this research (Saiki et al, 1988a,b). Recent progress toward the characterization of the hereditary acetylation polymorphism has also been made through the cloning of the arylamine N-acetyltransferase genes from the chicken (Ohsako et al, 1988), and from the rabbit (D.M. Grant and U. Meyer, personal communication). We may thus foresee knowledge of the human acetylation polymorphism extended soon to include the sequences of the rapid and slow acetylator genes of humans, and the development of improved procedures for the determination of the human acetylator phenotype and genotype based on this information.

III. SUMMARY

The human acetylation polymorphism has been known for more than three decades since its discovery during the metabolic investigation of the antituberculous hydrazine drug, isoniazid. The trait was originally known as the "isoniazid acetylation polymorphism" but is now usually abbreviated to the "acetylation polymorphism" because the acetylation of numerous hydrazine and arylamine drugs and other chemicals (Fig. 1) are subject to this trait.

A. Individuals phenotype as "slow" acetylators, homozygous for the slow acetylator gene, or "rapid" acetylators either heterozygous or homozygous for the rapid acetylator gene. Differences in individual acetylating capacity are ascribed to differences in the activities of the arylamine acetylating enzymes (isozymic N-acetyltransferase variants) of the liver, intestinal mucosa and certain other tissues. The chromosomal locus of the human gene has not been determined, but linkage analysis in mice indicates that the N-acetyltransferase gene is closely linked to Esterase-1 on mouse chromosome 8.

Recommendation: 1) That the chromosomal locus of the human acetylator gene(s) be determined.

B. The acetylator phenotype is a lifelong, stable characteristic of the individual that can be determined by procedures using any of several test agents (eg, caffeine, isoniazid, sulfamethazine, sulfapyridine). All suitable test agents discriminate rapid and slow acetylator phenotypes, whereas caffeine enables homozygous and heterozygous rapid acetylators to be discriminated from each other and from slow acetylators. These procedures can be

used with confidence to determine the acetylator status of healthy adults and children but caution is necessary in interpreting this information for infants, in altered physiologic states and in the presence of certain diseases and environmental substances.

Recommendations: 1) That investigators should strongly consider the use of the caffeine test for acetylator phenotype determination in human epidemiologic studies of acetylation because of its advantages over other test agents that are available.

2) That efforts to determine the structure of the acetylator genes responsible for the human acetylator polymorphism, and to determine the genes responsible for the hereditary acetylator polymorphisms in animal models for the human trait be continued apace with efforts on the human system.

3) That an improved test to determine the acetylator status utilizing that information and current molecular biology approaches and techniques applied to tissues that are readily available in human subjects (eg, leukocytes) be developed at a high priority.

C. The hereditary acetylator status of individuals provides valuable information about their therapeutic, pharmacologic and toxicologic responses and is a prognosticator of unusual susceptibility to toxicity from drugs widely used for the treatment of diverse diseases. More recently, the acetylator status has been implicated as an important factor modulating individual susceptibility to chemically induced cancer.

An extensive series of epidemiologic studies, particularly of persons occupationally exposed to arylamines, shows a statistically significant association between the *slow acetylator* phenotype and urinary bladder cancer. More limited information shows a significant association between the *rapid acetylator* phenotype and colorectal cancer. Isolated studies suggest that the acetylator status may be implicated as a susceptibility factor in cancer of the pharynx, larynx and stomach. One additional study suggests that prolonged use of permanent arylamine hair dyes by older women may favor the development of breast cancer in this subset of breast cancer patients although the effect of the acetylator status on the outcome was not evaluated.

Recommendations: 1) That appropriate epidemiologic studies be designed and conducted to determine the validity of the putative association of the acetylator status to colorectal cancer, and to other cancers, particularly of the gastrointestinal tract and associated structures.

2) That appropriate epidemiologic studies be designed and conducted to test the validity of the association of prolonged hair dye use and breast cancer, particularly in older women, and that an assessment of the importance of the acetylator phenotype be incorporated into those studies.

3) That samples of target tissues and cell lines be collected and banked as a resource for epidemiologic investigation of the role of the acetylation polymorphism and other hereditary metabolic polymorphisms in human cancer.

4) That wherever possible, these studies should be prospective to avoid or minimize the effect of the disease process on the relationships to be assessed.

D. Mechanistic studies of the metabolic activation of arylamine carcinogens and studies of nuclear DNA damage induced by arylamine carcinogens in intact animals, in tissues, and in cells isolated in culture from animal models expressing a hereditary acetylation polymorphism, including rapid and slow acetylators congenic inbred mouse strains, provide strong support for the human epidemiologic observations. Additionally, animal studies show that several metabolic steps in the metabolic activation of arylamines other than acetylation, including N-hydroxylation, sulfation, and deacetylation, are subject to appreciable genetic variation.

Recommendation: 1) That appropriate experimental models which express the hereditary acetylation polymorphism be constructed; and that they be used to supplement and facilitate the studies of human systems under investigation to identify and assess the effects of other hereditary metabolic factors that influence individual susceptibility to arylamine carcinogenesis.

E. The utility of DNA- and protein-arylamine carcinogen adducts as quantitative predictors of exposure and risk of arylamine-induced cancer in rapid and slow acetylators is unknown. However, several new and highly specific techniques of great sensitivity are available and investigations now in progress should aid in assessing this relationship.

Recommendation: 1) That parallel prospective investigations in humans and experimental animals that take account of hereditary differences in acetylation and take advantage of up-to-date technologies be designed to explore the utility of DNA- and protein-arylamine carcinogen adducts as aids to quantitative predictors of exposure and risk in humans.

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CHAPTER 3

Fragile Sites, Genomic Rearrangements and Cancer Predisposition

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In 1960, four years after the correct number of human chromosomes was established, Nowell and Hungerford [1] discovered an abnormally short chromosome 22, the "Philadelphia chromosome," in patients with chronic myelogenous leukemia. The development of banding techniques for metaphase chromosomes in 1970 permitted detailed exploration of chromosome structure and led to the finding of several chromosomal defects in different types of malignancy (for review, see ref. 2). Nevertheless, approximately half of the patients with acute leukemia and malignant solid tumors were thought to have normal chromosomes, due in part to the limited resolution of early banding techniques [2].

Technical advances in chromosome banding and cell culture made in the 1970s [3] have resulted in the finding of specific genomic rearrangements in a growing number of human cancers over the past several years. Although the genomic mechanisms involved in these rearrangements remain to be elucidated, for the most part critical clues are being uncovered in a number of different malignancies [4, 5]. At present, more than 80 types of leukemia, lymphoma and solid tumor have been found to have a recurrent genomic defect [4], and in most patients with acute leukemia and preleukemia and some with non-Hodgkin lymphoma, these defects can serve as critical prognostic guides because they indicate the severity of the disease and how well or poorly patients may respond to present therapies [6, 7].

FRAGILE SITES ARE TARGETS OF DIVERSE AGENTS THAT DAMAGE DNA

In 1983, we proposed that fragile sites on chromosomes may serve as vulnerable regions at which the breakpoint of chromosomal rearrangements found in human cancer are likely to occur [5]. A year later our laboratory reported the finding of a family of 51 constitutive fragile sites (c-fra) located at very precise homologous sites in the chromosomes of humans, chimpanzees and gorillas [8]. These evolutionarily conserved sites are expressed as chromosome breaks or gaps when cells are cultured in media deficient in folic acid and thymidine, or when cells cultured in standard media are exposed to the

antifolate drug fluorodeoxyuridine (FdU). Their expression is dramatically enhanced when cells are also treated with caffeine, a possible DNA repair inhibitor [9]. The c-fra were found to map at or close to one of the two breakpoints found in 24 of 31 specific structural chromosomal defects known in cancer, including several solid tumors [8]. Since several of the 51 c-fra, when analyzed under the microscope, appeared to coincide with a heritable fragile site (h-fra) that had been previously described, we suggested that an h-fra may represent a mutation of a c-fra [8]. In contrast to c-fra, h-fra occurs at a frequency of less than 0.2% each in the general population and are expressed heterozygously in a mendelian codominant fashion [10]. Except for sites 10q25.1, 16q22.1 and 17p12, the expression of h-fra also is related to inhibition of thymidilate synthetase, resulting in thymidine deprivation. Like c-fra, their expression is elicited by culturing cells in folic acid, thymidine-deficient media or by exposing them to a thymidilate synthetase inhibitor such as FdU [11]. However, h-fra are more highly expressed than c-fra and can be found in 10–50% of cells cultured in low folate media [10, 11], whereas c-fra generally are expressed at a much lower level (3–17% in cells with FdU and caffeine) [8]. Interestingly, h-fra 7p11.2, 11q13.3, 11q23.3, 12q13.1 and 16q22.1 coincide with breakpoints in specific defects described in leukemias and non-Hodgkin lymphomas (Fig. 1) [5, 8].

Recently, using 16 different mutagens and carcinogens plus caffeine as a mutagen enhancer, our laboratory found a total of 110 fragile sites in the human genome (Fig. 2) [12]. The agents used are from eight different types of agents (alkylating agents, antifolates, N-nitrosamines, aromatic hydrocarbons, halogenated hydrocarbons, antibiotics, α -polymerase inhibitors and gamma radiation, Table 1). Fourteen of 16 mutagens tested attacked between 70 and 74 of the 110 fragile sites, and agents that belong to the same class of mutagen tended to break the same sites (eg, the antifolates FdU and methotrexate attacked 85% of the same sites, while agents from other classes showed a lower degree of concordance (Table 2) [12, 13]. Strikingly, of the 110 fragile sites, 50 were found to coincide with the location of 75 cancer chromosome breakpoints, and 21 with the location of oncogenes that have been mapped to a chromosome band or subband (Fig. 2) [12]. The finding that diverse mutagens and carcinogens known to act through different molecular mechanisms induce a large number of chromosomal breaks at fragile sites suggests that such sites are general targets of mutagenic action and that mutagens and carcinogens may often induce genomic rearrangements as well as point mutations.

FRAGILE SITES ARE HOTSPOTS FOR CHROMOSOMAL REARRANGEMENT AND RECOMBINATION

When cultured lymphocytes from normal adults were exposed to the mutagens aphidicolin and FdU and the carcinogens gamma radiation and

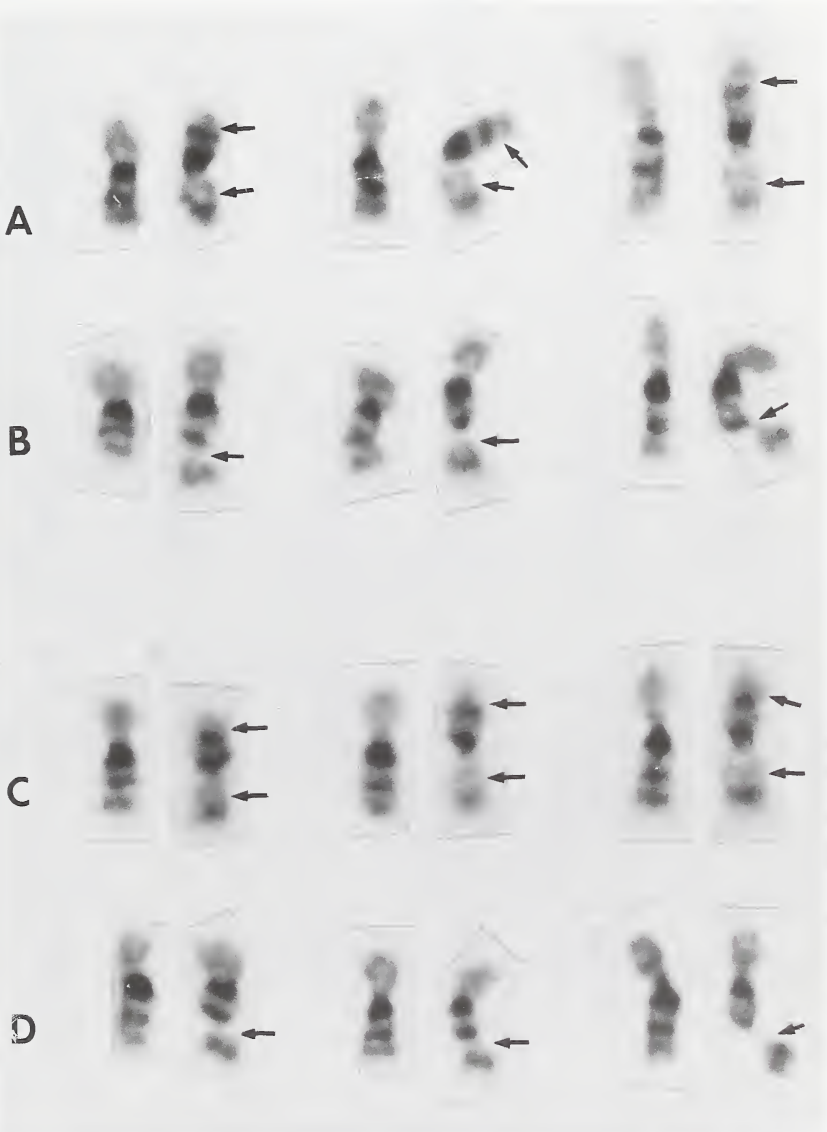


Fig. 1. *A* and *C*. Selected pairs of leukemic marrow chromosomes from two patients with $\text{inv}(16)(\text{p}13\text{q}22.1)$ at different stages of chromosome condensation. Arrows indicate breakpoints. *B* and *D*. Selected pairs of cultured normal lymphocytes illustrating the presence of a heritable fragile site 16q22.1 (see arrows). In patient *A*, *B* the chromosome 16 with a large polymorphic pericentromeric heterochromatin is involved in the expression of the fragile site and the inversion. (From Yunis: *Cancer Genet Cytogenet* 11:125, 1984, with permission.)

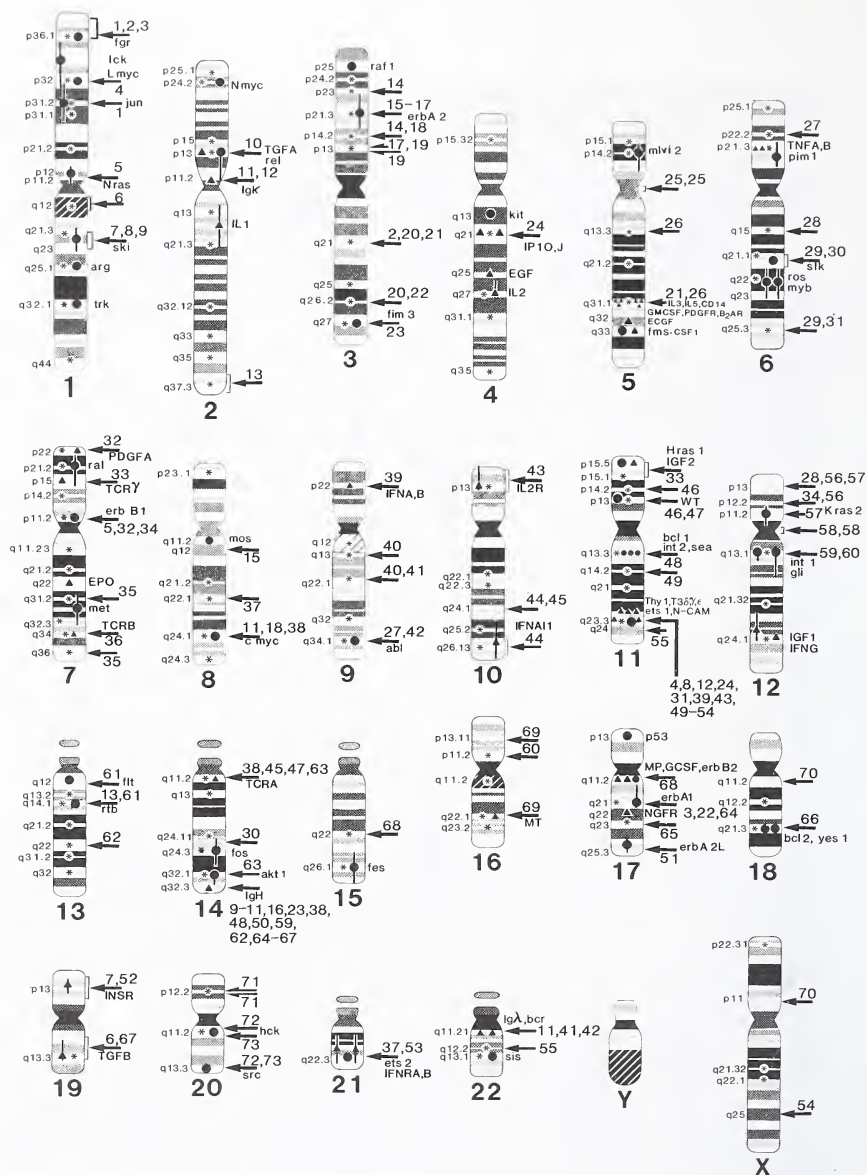


Fig. 2. Human chromosomal map depicting approximately 650 Giemsa bands, 110 constitutive fragile sites (*), 50 oncogenes (●), 44 growth-factor or active genes of differentiated cells (▲), and 2 breakpoints for each of 70 of the 73 specific structural chromosome defects found in various neoplasias (←). Pertinent bands are marked on the left of each chromosome, and names of oncogenes, growth-factor genes and cell-differentiation genes on the right. When an oncogene, growth-factor gene or active gene of a differentiated cell is mapped to a small chromosome region rather than a band, ♦ or ♦ is used. When the precise location of a cancer breakpoint is uncertain, J— is used. For the specific structural chromosome defect associated with each of the 73 numbers, see ref. 4. For meaning of symbols used for oncogenes, growth-factor genes and cell-differentiation genes and their location, see ref. 63. (From ref. 63. with permission.)

TABLE 1. Mutagens/Carcinogens Tested

Agents Tested	Fra Test	Ames Test	Carcinogen Test
Actinomycin D	+	—	+
Aphidicolin	+		+
Benzene	+	—	+
Bleomycin	+	—	
Bromoacetaldehyde	+		+
Busulfan	+	+	+
Carbon tetrachloride	+	—	+
Chlorambucil	+	+	+
Cytosine arabinoside	+	—	
Diethylnitrosamine	+	+	+
Dimethyl sulfate	+	+	+
Distamycin A	+		
5-Azacytidine	+	+	
Fluorodeoxyuridine	+	—	
γ -Radiation	+	—	+
Methotrexate	+	—	
Control Substances			
Anthracene	—	—	
Acetone	—	—	
Dimethyl sulfoxide	—	—	
Mannitol	—	—	
12-myristate 13-acetate diester (TPA)	—	—	

busulfan, it was found that a number of chromosome defects were elicited (Fig. 3). Some of the defects were microscopically indistinguishable from those found in several different types of neoplasia including acute leukemia, preleukemia and non-Hodgkin lymphoma [12]. We found 41 examples of somatic pairing of homologous chromosomes with exchange of chromatids at fragile sites and these involved 15 of the 23 human chromosome pairs [12]. These findings provide physical evidence for the molecular discoveries in

TABLE 2. Concordance in Fragile Site Expression Among Selected Mutagens and Carcinogens^a

	Fluorodeoxyuridine	Chlorambucil	Dimethyl Sulfate	Gamma Radiation	Carbon Tetrachloride
Methotrexate	85%	62%	54%	59%	50%
Busulfan	63%	80%	75%	69%	50%
Bleomycin ^b	61%	64%	67%	77%	49%
Benzene	61%	51%	52%	47%	69%
Bromacetaldehyde	61%	51%	54%	51%	62%

^aFor specific fragile sites expressed see Yunis, Soreng and Bowe, 1987. Compounds belonging to a given class of mutagen, such as the alkylating agents busulfan and chlorambucil, express similar fragile sites with approximately 80% concordance. Dissimilar agents such as methotrexate and carbon tetrachloride often have a concordance of approximately 50%.

^bRadiomimetic agent. (From ref. 13, with permission.)

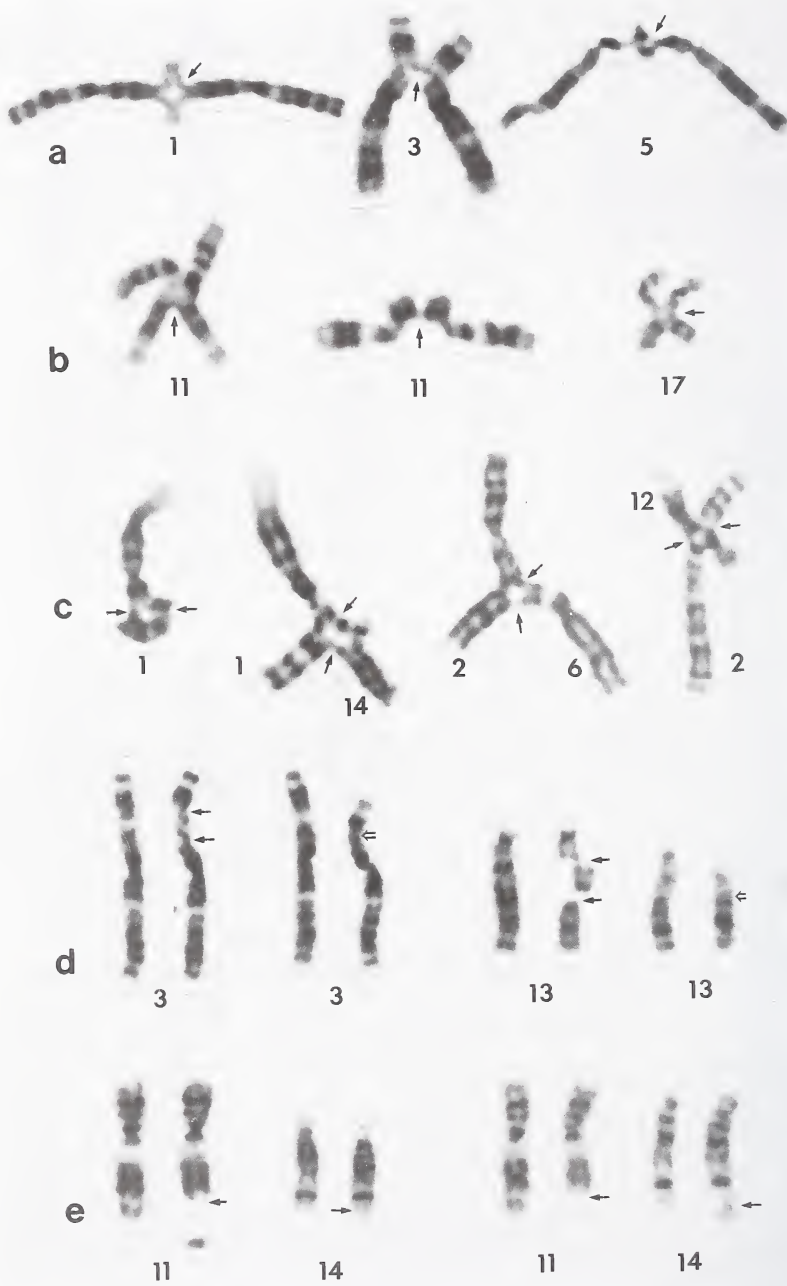


Figure 3

retinoblastoma and Wilms tumor. In these diseases, chromosome band 13q14 and 11p13, respectively, may often look microscopically normal but in the tumor cells the affected locus has been reduced from heterozygosity to homozygosity [14, 15] as might occur through somatic exchanges of this type. Homologous chromosome exchanges at homologous fragile sites also may prove to be the same as those occurring in meiotic recombination and through which genetic diversity is created. A comparison of chiasmata recently reported in human spermatocytes [16] with fragile sites [12] shows a correlation between approximately half the sites involved in meiotic crossing-over events and fragile sites induced by antifolate drugs. In addition, highly polymorphic DNA minisatellites, believed to play a role in the generation of new length alleles during meiosis [16a], were recently mapped to sites of crossing-over in human meiotic chromosomes [16b] and to bands containing fragile sites in human mitotic chromosomes [16c]. Thus, a class of fragile sites may play a role in both meiotic and mitotic recombination.

Additional evidence that recurrent genomic rearrangements may arise from the expression of fragile sites comes from several laboratories. Using somatic human-Chinese hamster cell hybrids and DNA analysis of genes that flank the human fragile X, investigators showed that the breakpoint of FdU-induced human-rodent translocations involving the h-fra Xq27 was within 10 cM of the flanking probes [17]. In similar experiments, others showed that the human fragile site Xq27 and the fragile site 3p14 can be induced by FdU or aphidicolin to form fragile-site-specific rearrangements with Chinese hamster chromosomes [18]. Together with our evidence for chromosomal rearrangements and homologous recombination produced via fragile sites [12], the evidence suggests that fragile sites are mutagen-inducible "hotspots" for recombination and rearrangement and that they conceivably could be involved in specific chromosome translocations and deletions *in vitro* and *in vivo*.

Malignancies with a specific reciprocal translocation or inversion have consistent chromosomal breakpoints and very often correlate with the location

Fig. 3. The first two rows show examples of somatic pairing and recombination of homologous chromosomes observed after exposure of normal cultured lymphocytes to aphidicolin (a) and busulfan (b). c: Examples of intrachromatid exchanges involving chromosomes 1q and 14q, 2q and 6p, and 2p and 12q, respectively, all induced by aphidicolin in normal cultured lymphocytes. d: Selected examples of mutagen-sensitive sites and chromosome defects induced *in vitro* when normal cultured lymphocytes were exposed to γ -radiation. The deletion (3) (p14.2p23) is frequently seen in small cell carcinoma of the lung, and the deletion (13) (q13.2q21.3) can be seen in retinoblastoma. e: Mutagen-sensitive sites 11q23 and 14q32.3, followed by a t(11;14) (q23;q32.3), seen in diffuse large-cell lymphoma and induced by γ -radiation in a pre-B cell line. For further details, see ref. 12.

of fragile sites, oncogenes and other critical cell-differentiation genes of specific cell types [4, 12]. In contrast, most malignancies with a recurrent chromosomal deletion have breakpoints that show some variability [5, 13]. Some of these breakpoints involve mutagen-sensitive fragile sites. For example, in acute myelogenous leukemia and preleukemia a deletion 7q often involves breakpoints at q31.2 and q36, and less frequently at q21.2, q32.3 and q34 [4, 5, 19]. Fragile sites at these breakpoints are expressed when cells are exposed to solvents, such as benzene, or therapeutic agents, such as cytosine arabinoside and gamma radiation [12, 13]. These agents have been implicated in patients with primary or secondary leukemia or preleukemia who have a deletion 7q in their malignant cells [20].

Other defects produced *in vitro* included a deletion involving band 13q14 as seen in retinoblastoma and a deletion 3p14.2p21 observed in small cell lung cancer (Fig. 4) [12]. The interstitial deletion 3p has been reported with variable breakpoints at p14.2, p21, and p23, [21] all of which correspond to fragile site bands. Fragile site 3p14.2 is the most sensitive constitutive fragile site and is highly expressed with agents such as benzene, benzo(a)pyrene and nitrosamines in man, chimpanzee and gorilla (Fig. 4) [8, 12, 13]. Since these agents have been found in tobacco smoke [22] and tobacco has been implicated as a causal agent in one third of all cancers in the United States, the structure of fragile site 3p14.2, as well as 3p21 and 3p23, should be a focal point of investigation to elucidate possible differences in the fragile site DNA sequences between cigarette smokers who develop and those who do not develop cancer. Such investigations should be spurred by the finding of a higher expression of fragile site 3p14.2 in the blood cells and bone marrow of cigarette smokers compared to nonsmokers [23].

Our finding that mutagens and carcinogens consistently break chromosomes at fragile sites, in turn eliciting somatic recombination, strongly suggests that mutagens can act by inducing genomic rearrangement and recombination. Caffeine-enhanced fragile site expression could form the basis of a sensitive *in vitro* mutagenesis testing system that can accurately determine the recombinational capacity of human chromosomes when exposed to genotoxic agents (Table 1). Such a test could prove to be a useful complement to the widely used Ames test that assays the ability of various agents to induce point mutation in *Salmonella* (Table 1) [23a].

FRAGILE SITES AND HYPERSENSITIVE CHROMATIN SITES

Intrigued by these findings and by the fact that several mutagens tested (dimethyl sulfate, bromoacetaldehyde, gamma radiation) are known to induce chromatin hypersensitivity in regulatory regions of active genes [24-27], we asked whether fragile sites might represent regions of genomic activity. Using a novel technique, the nucleolytic enzymes DNase I and the restriction

Fragile site 3 p14.2

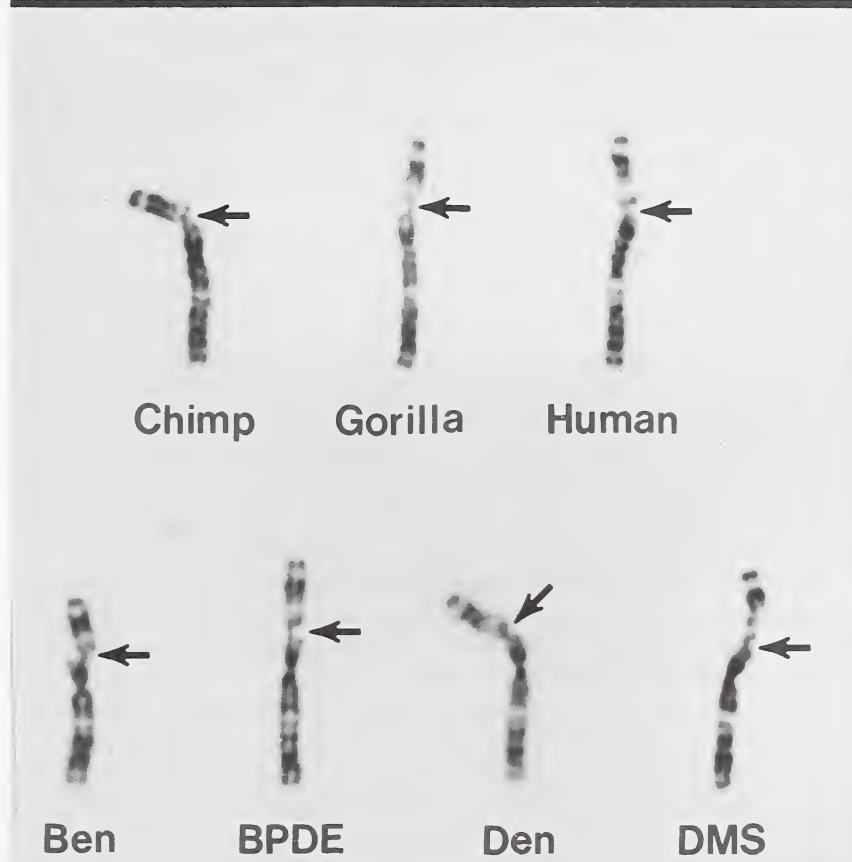


Fig. 4. Fragile site 3p14.2 is conserved through human evolution (top row) and expressed by a variety of different carcinogens (bottom row) including benzene, benzo(a)pyrene-diol-epoxide, diethylnitrosamine and dimethyl sulfate. This highly expressed fragile site may be involved in the deletion 3p found in small cell lung cancer. Ben, BPDE, and DEN are present in tobacco smoke. (From ref. 13, with permission)

enzymes *Sma* I and *Sph* I that target GC-rich sequences were introduced into living cells to express fragile sites [28]. *Sma* I recognizes the sequence CCC-GGG frequently found in GC-rich promoters such as those of *H-ras*, *K-ras*, *pim-1*, epidermal growth factor receptor and transforming growth factor beta [29–31]. The sequence targeted by *Sph* I (GCATG-C) is interest-

ing because it can form Z-DNA which in turn can destabilize the DNA double helix when attacked by mutagens [32]. Separate cultures were exposed to the classic carcinogen benzo(a)pyrene diol-epoxide (BPDE), which is also known to induce hypersensitive chromatin sites in regulatory regions [33].

Together, the four agents induced 105 recurrent break sites of which 67 correlated with 110 fragile sites previously found (61%) when PHA-stimulated, cultured T-lymphocytes were exposed to 16 different mutagenic agents [12, 28]. When fragile sites expressed separately by BPDE, DNase I, *Sma* I and *Sph* I were compared with each other and with previously characterized fragile sites, it was found that 47 of the 75 DNase I sites (63%) correlated with mutagen-induced sites [28]. Also, 47 of the 73 sites induced by BPDE (64%) correlated with DNase I sites. Because BPDE, like DNase I, is thought to act on regulatory regions of active genes [33], we compared *Sma* I and *Sph* I sites with DNase I and/or BPDE sites. This comparison showed that 52 of 55 *Sma* I sites and 45 of 48 *Sph* I sites correlated with DNase I and/or BPDE sites. Also, 85 mapped oncogenes, growth-factor genes and cell-differentiation genes important in cancer have been mapped to 56 chromosome band sites [4] and 39 (70%) of these correlated with DNase I and/or BPDE sites. Finally, when BPDE and DNase I, *Sma* I and *Sph* I were compared together, it was observed that 50 of 105 sites (48%) were elicited with at least three of the four agents [28].

These findings suggest that a large class of chromosomal fragile sites may be highly sensitive to certain nucleolytic enzymes, specific restriction enzymes and carcinogens because they are sites of active genes. The possibility that chromosomal fragile sites may be related to oncogenes, hypersensitive chromatin sites and cancer is also suggested by the finding that in mouse and chicken, oncogenic viruses are preferentially integrated into chromosomes at promoter regions of oncogenes such as *c-myc*, *c-erb B*, *c-myb* and *pim-1* [30, 34, 35] and at hypersensitive chromatin sites in virus-induced leukemia and lymphoma in mice and chickens [36, 37]. These oncogenes have homologous loci in human chromosomes and at least one of them (*c-myc* at band 8q24.1) is localized at a fragile site band (Fig. 2). Further, the sites of integration of human adenovirus 12, simian virus 40, human papillomavirus 18, hepatitis B virus and Epstein-Barr virus have been recently localized to specific chromosome bands in human cells [38-43]. It is intriguing that many reported sites of integration correlate with fragile site bands, which may contain genes that are targeted for virally induced transcription. Molecular study should determine whether a correlation actually exists.

Taken together, these findings suggest that fragile sites may be general targets of mutagenic action and may contain DNA sequences critical in gene regulation. These sequences may include the recombination nonamer (GGTTTTTGT) and heptamer (CACTGTG) sequences involved in immuno-

globulin and T-cell receptor rearrangements [4], the related hexanucleotide GGTTTC associated with deletions of beta globin and albumin in humans and rodents [44], CACA sequences believed to be involved in general somatic recombination from viruses and yeast to man [45], and multiple GC boxes in the promoter region of growth factors, oncogenes and housekeeping genes [29–31].

AGING, DIET, FRAGILE SITES AND PREDISPOSITION TO CANCER

Indirect evidence has emerged suggesting that a relationship may exist between age, carcinogens, diet, fragile sites and cancer. For example, chromosome damage resulting from folate or vitamin B₁₂ deficiencies has been recognized since investigators initially described aberrant chromosomes and chromatin breaks in patients with megaloblastic anemia [46]. Since a large number of fragile sites can be induced by low folic acid or the antifolates fluorodeoxyuridine and methotrexate [8, 12, 47], it is reasonable to speculate that certain nutritional deficiencies may play a role in DNA instability *in vivo*. This may be especially true of older people who have a relatively higher expression of fragile sites [28, 48, 49]. Alcohol consumption has been found to be a risk factor for esophageal, rectal, lung and breast cancer in several recent studies [50–52]. Also, tobacco smoke, particularly in combination with age and alcohol, has been implicated as a causal agent in one third of all cancers in the United States [50, 53]. Interestingly, smokers typically have lower levels of circulating folate and vitamin B₁₂ than nonsmokers [54] and recently it was found that supplemental folic acid and vitamin B₁₂ significantly reduced atypical bronchial squamous metaplasia, a premalignant lesion, in long-time smokers [55].

In our earlier studies, several patients with leukemia or lymphoma were found to have an increased rate of chromosomal breakage at a fragile site in their normal cells that corresponded to a chromosome breakpoint in their tumor cells (Fig. 1) [5, 8, 56]. This suggested to us that some change in the fragile site might predispose to cancer and that individuals with a more labile fragile site might be at greater risk. For example, the heritable fragile site 16q22.1 has been found in the lymphocytes of patients with AML with an *inv*(16) (p13q22.1) (Fig. 1) [5, 56–58]. Also, a heritable distamycin A-inducible fragile site 11p15.1 has recently been reported in two patients with acute myelogenous leukemia and a chromosome translocation *t*(7;11) (p15-p13; p15) [59]. Furthermore, in a study of cells isolated from patients with leukemia and lymphoma, elevated expression of specific *c-fra* was found in the normal lymphocytes of patients that corresponded to one of the breakpoints of the chromosomal rearrangement seen in their malignant cells [8]. It should be stressed, however, that not all patients with certain specific chromosome defects such as *inv*(16) (p13q22.1) are carriers of a heritable fragile site (for reviews, see Cancer Genetics and Cyto genetics 31:1–146, 1988), and relatives

of leukemic patients with a rearrangement in the same chromosome band as an h-fra may not be predisposed to cancer [59a]. Larger studies of families are needed, including those in which one or more members express an h-fra, to determine whether h-fra predisposes to cancer in patients with a chromosomal rearrangement at an h-fra band in their malignant cells. The DNA sequences involved in h-fra and c-fra need to be elucidated with the aid of pulsed-field gel electrophoresis and sequence analysis before any conclusions can be drawn as to whether either or both are involved in cancer predisposition at the molecular level.

MOLECULAR INVESTIGATION OF FRAGILE SITES

One of the more common breakpoints of specific chromosome rearrangements found in patients with leukemia and lymphoma occurs at band 11q23.3 [60]. Interestingly, 11q23.3 is also a band where a heritable (rare) as well as constitutive (common) fragile site has been found [8]. Recently, we established the order of several genes in band 11q23 using transverse alternating field electrophoresis and Southern blots of somatic-cell hybrids (Fig. 5) [61]. We have narrowed the location of both the cancer breakpoint and the constitutional del (11) (q23qter) likely derived from the h-fra 11q23.3 to a region between the CD3 γ and *ets-1* genes spanning at most 280 kilobases of DNA on a *Cla* I restriction site [61]. We hope to learn in the near future whether the 11q23.3 cancer breakpoint and fragile site coincide and, if so, the key DNA sequences involved.

A related area of interest would be to explore fragile site expression in different tissues and different stages of cell differentiation to learn why certain agents and cell types are more efficient than others in rearranging genomic

Fig. 5. Proposed gene order, amplification and distance in kilobases of genes on the long arm of human chromosome 11, using breakpoints of selected chromosomal rearrangements.

*The abbreviations used are as follows: *bcl-1* (B-cell leukemia/lymphoma oncogene), PGR (progesterone receptor), CLG (collagenase), N-CAM (neural cell adhesion molecule), apo (apolipoprotein), CD (cell differentiation antigen), *ets-1* (E26 erythroleukemia oncogene), Thy-1 (T-cell surface antigen), PBGD (porphobilinogen deaminase), and SRPR (signal recognition particle receptor). The broken line indicates uncertainty as to gene order.

**Homogeneous staining region in a patient with acute myelomonocytic leukemia. The length of the amplicon region could prove to be smaller than indicated, if a recombinational deletion event took place between some of the genes.

†Constitutional deletion (11) (q23.3qter) in a patient whose mother and brother have h-fra 11q23.3. (From ref. 61, with permission).

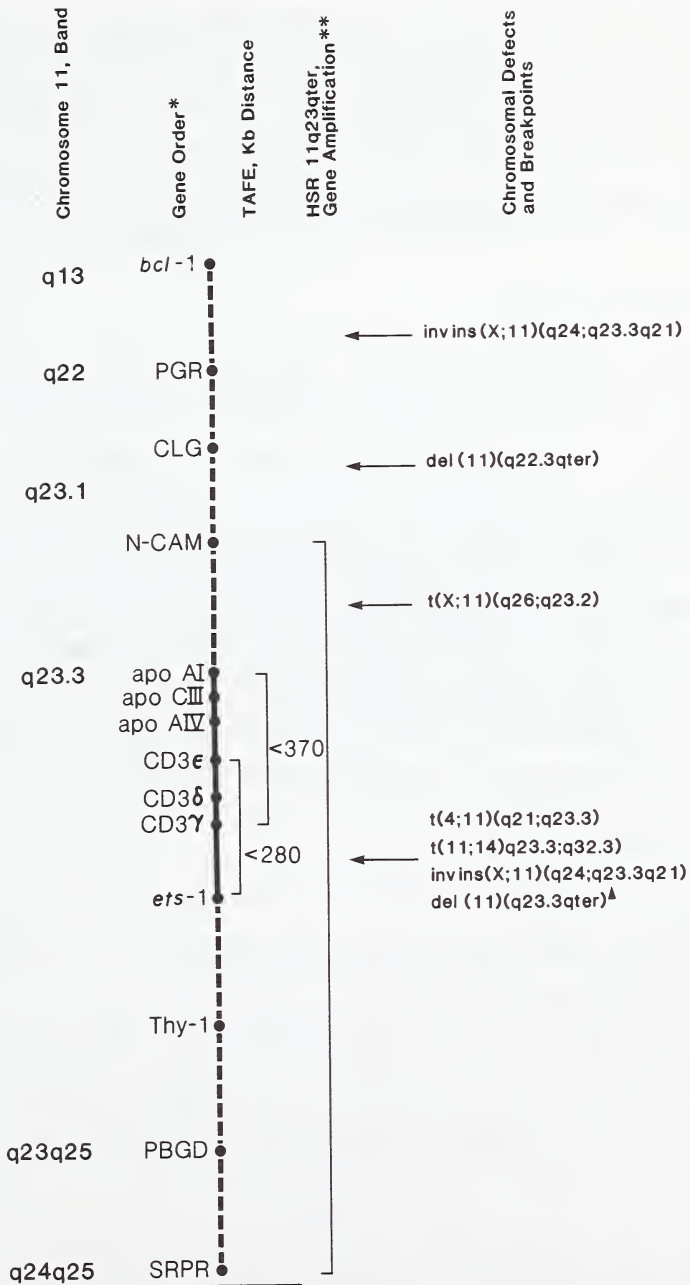


Figure 5

segments in different cancers. Preliminary evidence suggests that there are similarities and differences in fragile site expression when T and B lymphocytes, fibroblasts and bone marrow cells are tested with agents such as FdU, dimethyl sulfate and bromocacetaldehyde (unpublished observations). The fact that diverse mutagens and carcinogens break chromosomes not only at common sites but also at distinctive ones suggests that certain fragile sites may be more sensitive to a given agent in certain tissues and this could conceivably relate to their potential to induce specific types of neoplasia [62].

RECOMMENDATIONS

The high correlation between the mapped location of oncogenes, fragile sites and cancer chromosome breakpoints is intriguing and calls for molecular investigation to determine whether certain classes of sequences, such as minisatellite core sequences [45a], may be involved in fragile site-mediated rearrangement and recombination observed *in vitro* [12]. The possibility that a class of fragile sites also may have a high correlation with chromosomal sites involved in meiotic crossing-over [16] suggests further that fragile sites may play a role in the creation of genetic diversity. Although these cytologic correlations need to be elucidated at the molecular level, our initial investigation of chromosome subband 11q23.3 by pulsed-field gel electrophoresis indicates that h-fra 11q23.3 and a cancer chromosome breakpoint(s) 11q23.3 occur on the same restriction fragment [61]. Further analysis will determine whether they coincide and whether fragile sites in general serve as predisposition factors or are otherwise involved in human malignancy.

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CHAPTER 4

The Chromosome-Breakage Syndromes: Rare Disorders That Provide Models for Studying Somatic Mutation

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INTRODUCTION

Stability is a cardinal feature of the genetic material; yet, mutability is another. The analysis of the various metabolic processes and chromosomal mechanisms that ensure stability constitutes a major area of cell biology. And, germline mutation is the basis for the variation that simultaneously provides substrate for evolution of species and the object for study in classical genetics.

But, mutation occurs in somatic as well as in germline cells. There, however, it has received relatively little attention. That is changing now that somatic mutation, especially chromosome mutation, generally has come to be recognized as etiological in neoplastic transformation, and probably in tumor progression as well. Here I shall address somatic rather than germline mutation.

I shall advance as models for study certain heritable disorders in which the two cardinal features of the genetic material mentioned above are disturbed, in a different and interesting way in each disorder. As a group, these disorders display genetically determined increased instability of the genetic material itself in somatic cells, and, consequently, an increased frequency of somatic cell mutation. These clinical disorders sometimes are grouped and referred to as the chromosome-breakage syndromes, some of them specifically as the DNA-repair defects. Because they are recessively transmitted, each represents a variation from normal in a single biochemical pathway. Thus, they constitute instructive models for exploring and dissecting the several mechanisms whereby somatic mutations arise and for analyzing the variety of mutations that occur. Furthermore, because at least in cells from some of them, mutations at many, perhaps all, loci in the genome are occurring at an accelerated rate, they increase the chance for studying experimentally the effects of specific mutations on cellular function. The effect on cellular function that mainly has drawn attention to them recently, and that will be emphasized here, is neoplastic transformation; but, they may deserve study as well in relation to other time-dependent "degenerative" processes that affect

human health. Neoplastic transformation has been the main effect studied because of the dramatic increase in clinical cancer in persons with each one of the syndromes. Affected homozygotes have many other interesting features, however, and their continued clinical scrutiny should indicate whether they can serve as experimental models for other human diseases in which somatic mutation has been overlooked as an etiological factor of importance (a matter not addressed further here).

MUTATION IN SOMATIC CELLS—ENDOGENOUS AND EXOGENOUS

The sources of mutation in somatic cells are two. One to some extent theoretical source is error that occurs during normal cellular metabolism that leads to alterations in the DNA. If just a few of the numerous and diverse biochemical reactions and complicated mechanical activities in which DNA engages normally during both the intermitotic and mitotic stages of the cell cycle are error prone, many errors potentially might alter the DNA. If, when, and how often such endogenous mutagenic errors arise is poorly understood—and little studied. The other source of mutation, about which much is known, is error induced by environmental agents that either directly or indirectly lead to alteration of the DNA, and the literature is vast describing DNA-damaging agents, their effects on the genetic material, the various lesions they induce, and the different repair mechanisms the different lesions invoke.

The frequency of somatic mutations. Assays of the number of mutations that exist in cells that populate proliferating tissues of normal persons suggest either that the diverse biochemical reactions and activities in which DNA is involved are relatively error-free or else that most of the errors that do occur are either repaired accurately or result in cell death. Furthermore, the potential DNA-damaging effects of environmental mutagens we regularly encounter must in general be nullified. These conclusions are based on the results from the few laboratory test systems that have been devised to estimate the number of mutations that accumulate *in vivo* in persons that have not been exposed excessively to mutagenic environmental agents. The test systems fall into two classes. In the first class, the number of mutations of various types that have affected some specific locus are estimated in proliferating populations of cells: namely, (a) in blood lymphocytes, at the HPRT (hypoxanthine guanine phosphoribosyltransferase) locus on the X chromosome [1–3]; (b) in blood lymphocytes, at the HLA locus on chromosome No. 6 [4]; and (c) in blood erythrocytes, at the GPA (glycophorin A, or MN blood group) locus on chromosome No. 4 [5]. In the second class of tests, the numbers of large chromosome mutations are estimated, either in terminally differentiated cells by scoring cells with micronuclei in the desquamated epithelium of the oral or

urinary tract [6] or in proliferating populations by scoring cells with missing or extra whole chromosomes or with chromatid aberrations in freshly aspirated bone marrow in short-term culture or of lymphocytes, examining cells in their first mitosis following removal from the blood stream. The mutations at specific loci detected in normal persons using a test system of the first class are surprisingly few in number. Among blood lymphocytes $1-14 \times 10^{-6}$ is mutant at the HPRT locus and 2×10^{-6} to 7×10^{-5} at the HLA locus, and among erythrocytes $1-8 \times 10^{-5}$ is mutant at the GPA locus. In the second class of tests, those that detect large chromosome mutations, many of which would be genetically lethal (ie, permit no further cell-division cycles), the mutation rate is much higher: 3-5 exfoliated epithelial cells per 1,000 contain a micronucleus. The important point is that cells containing mutations do accumulate in the tissues of persons with no history of excessive exposure to DNA-damaging agents. These same test systems also show that mutant cells accumulate in increased numbers in individuals exposed excessively to environmental DNA-damaging agents. A recently devised molecular approach to the quantification of somatic mutation may also have detected an increased mutability of the human chromosomes with increasing age [7].

The causes of somatic mutation. How do mutation-inducing errors come about in cells? Both exogenous and endogenous causes can be envisioned (Fig. 1). Much study has been made of the enzymes employed by normal cells in repairing damage produced in DNA as result of cellular contact with exogenous agents. Even though repair mechanisms exist, mutations should on occasion arise (i) if the enzymes of a particular repair pathway are incapable of handling an excessive amount of damage that has been induced at some particular time, possibly permitting thereby a replication fork to encounter an unrepaired lesion from which a replicational error may occur, or (ii) if a particular repair pathway itself is error-prone.

Certainly damage to DNA responsible for the mutations that are detectable in healthy people in many cases would have been environmentally induced; some DNA-damaging agents are ubiquitous and part of man's modern environment, while others are recognized environmental mutagens that are subject to control. On the other hand, endogenous causes of mutation conceivably are more important than have been suspected previously. Unfortunately, however, relatively little is known about errors that occur spontaneously in normally functioning cells and that can lead to heritable alteration in the DNA. (Relevant here are Chapters 1 and 2 in this volume, dealing with genetic variations in the handling of ingested materials and the generation of mutagenic metabolic intermediates.) Of the mutations that do accumulate, the proportion due to such postulated endogenous vs exogenous mutagenic agents certainly is an unknown.

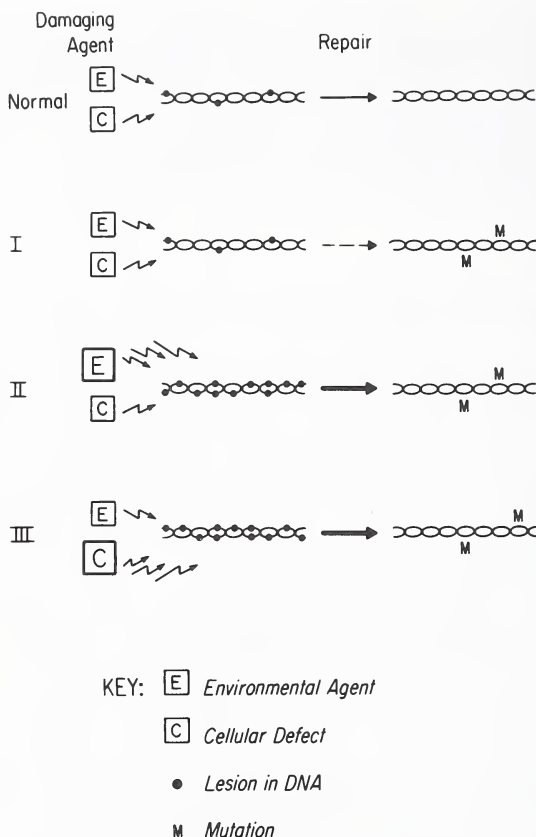


Fig. 1. Mutations shown as a consequence of erroneous repair of damaged DNA in cells defective in repair mechanisms (I), or overburdened with lesions as result of excessive damage from environmental (II) or endogenous (III) causes. Normally DNA can be damaged by environmental agents (E in the figure), but repair mechanisms restore the DNA to normal and mutations (M) ordinarily are not produced. (M symbolizes mutations both visible to the cytogeneticist and invisible; essentially all suitably studied clastogens (chromosome-breaking agents) are mutagens also, and vice versa.) Increasing E abnormally, as by excessive chemical or radiation insult to the cell, II in the figure, produces more lesions in the DNA; in this case, heavy duty will be required of repair mechanisms (the heavier arrow in the figure) and a few errors (M) will be made. In cells genetically defective in some repair mechanism (dashed arrow), I in the figure, mutations occur with abnormal frequency even with a standard environmental dose of mutagens. C represents cellular factors that are or may be present in normal cells. By themselves they can be responsible directly or indirectly for the appearance in DNA of substrates for repair mechanisms ("lesions" in the figure), also reparable as in the case of E-induced lesions. C, which is hypothetical, might be increased abnormally in

Experimental models. It is desirable, therefore, to know more about what must be an enormous number of DNA-surveillance and -repair pathways that are required for maintaining the integrity of DNA, even in cells not encountering environmental mutagens. Presumably, recessive mutation at any one of the myriad loci that specify the enzymes involved in these several pathways might occur and segregate in the population. Homozygosity for such recessive mutations, if not lethal during embryonic development, would be expected to result in what can be called mutator phenotypes; that is, either increased numbers of errors would occur in the tissues of such homozygous-affected individuals or errors that occur spontaneously would not be repaired promptly and/or accurately in them, the result being the accumulation with age of increased numbers of mutations at diverse loci throughout their genome. Do mutator phenotypes exist in man? Can they not be studied advantageously? The answer to both questions is, "Yes," as will be shown below.

Insight into the importance of maintenance of the integrity of DNA indeed has been gained from the study of several rare, heritable mutations in man that adversely affect the repair of damaged DNA—the DNA-repair defects—some details concerning which will be given below. However, by far the largest number of mutant genes that when homozygous lead to defective DNA-repair have been detected in experimental plants and animals, eg, in microorganisms, yeast, maize, and *Drosophila*. Several experimentally induced mutations that affect DNA repair or that in some way result in hypersensitivity to DNA-damaging agents in rodent cell lines, have been discovered [eg, 9–11], and the loci concerned with DNA repair, which as expected display a strong phylogenetic conservation, are being cloned and their products' actions analyzed. The most impressive aspect of the information obtained thus far pertains to the

the presence of the following: (a) genetically defective enzymes such as unwinding proteins, topoisomerases, polymerases, and ligases that would result in lesions through sluggishness or outright erroneous action in a pathway concerned with semiconservative DNA replication; (b) defects in some cellular process unrelated directly to DNA synthesis but which could result in the accumulation, either inside the cell or in extracellular fluids, of some substance normally present in insignificant quantity that in turn is capable of producing lesions in DNA; (c) defects that result in a quantitative imbalance, either an excess or a deficiency, of some essential nutritional component of a chromosomal protein or some precursor for synthesis of the DNA molecule. In any case, C is responsible for the generation of substrates on which repair systems will be invoked to act. III in the figure depicts excessive C, the result being, just as in II and I, an abnormally great number of M. As in II, the excessive burden of lesions would have made unusual demands on repair mechanisms—themselves normal and intact—, possibly including error-prone mechanisms. (Fig. 1 from Ref. 8, with permission.)

large number of loci in all the species examined that are concerned with maintaining the integrity of the genetic material. Many loci in *Drosophila* concerned with repairing UV damage have been identified. In hamster at least six complementation groups of loci concerned with UV-light-induced damage have been identified, and they complement mutants at the seven or eight human loci recognized so far to be concerned with that type damage, indicating that different mutant loci are affected [12]. Another example: for the chromosome mechanism sister-chromatid exchange, at least four loci in mouse [13] and two shared by hamster and man [14] are known to participate in maintaining its normally low rate.

In addition to the large number of non-human mutations that have been discovered, a few valuable models for use in the study of DNA damage and its repair also do exist in humans, each coming to the experimental laboratory from clinical medicine. And, here I adjoin to the disorders that clearly are defective at DNA repair—only for the xeroderma pigmentosum can this be said today—several others that for one reason or another also feature genomic instability. At least one of the mutations detected is of importance in maintenance of the integrity (stability) of the genetic material, but apparently is concerned primarily with normal DNA synthesis rather than with its repair. Each mutant human gene thus far recognized to be involved in some way with DNA repair or with the maintenance of chromosome stability is very rare. When present in the heterozygous state such mutations ordinarily go undetected, their presence in a phenotypically normal person's genome and that of his mate becoming apparent only upon the birth to them of a child with the abnormal phenotype. (Other mutant genes about which we know nothing may be presumed to be segregating in the human population, unrecognized because the homozygote is inviable.) A striking degree of genetic heterogeneity exists in the majority of these rare clinical disorders, a fact indicating that in man as in other species a large number of loci are involved in maintaining the genetic material intact. The human genetic disorders that feature genomic instability and that have been reasonably well-characterized are the subject of this chapter—Bloom's syndrome (BS), Fanconi's anemia (FA), ataxia-telangiectasia (AT), the Nijmegen breakage syndrome (NBS), xeroderma pigmentosum (XP), and Werner's syndrome (WS). Genetic heterogeneity has been demonstrated by complementation study in four of the six disorders, from which it is known that, at a minimum, 18 mutations, possibly at 18 different loci, are segregating in the human population: BS, 1; FA, 2; AT, 4; NBS, 2; excision-defective XP, 7; variant XP, 1; and, WS, 1. (BS appears to be genetically homogeneous, at least with respect to the locus mutated, but variant XP and WS as yet have not been examined for genetic heterogeneity since no appropriate test systems exist.)

It is significant that each of these rare human disorders is associated with an increased incidence of cancer. It should be emphasized at the outset, however, that even though affected homozygotes are predisposed to cancer development, the disorders as a group are so rare that they have little impact on the generality of human cancer. These disorders all are what might be called "good" recessives in that effects of carrying the genes in single (heterozygous) dose cannot in most of the cases be detected by sophisticated laboratory tests of function. In theory, however, the genes responsible for these clinical entities would play an important role in cancer etiology in the general population if heterozygous effects did exist, because although homozygotes are very rare, phenotypically normal persons carrying one of the many mutations collectively would be common. (This fact and potential value in the study of the question was recognized in the National Cancer Plan drawn up in 1971-72, in Objective 2, Approach 5.1 [15].) For several reasons, obtaining information about the effects, if any, of heterozygosity is not easy. The few surveys carried out might suggest that heterozygotes for some of these rare mutations do have an increased risk of developing cancer [16-19]. Actually, the health significance, if any, of carrying one of these mutations is unknown, but the question remains a tantalizing one, especially because of the fact that many normal persons must carry one of them.

In spite of the rarity of the disorders, increased understanding of them as clinical entities has come about recently. It is interesting to note that this improved clinical characterization of what had been diseases almost or totally unknown to many physicians has been generated mainly because of the interest in the diseases shown by human geneticists and basic biologists asking what light their study might shed on cancer etiology. Fortunately, the increased knowledge proves of much value to affected families because improved understanding of the pathophysiological processes responsible for the phenotypes, as well as the natural course of the disorders, has been an inevitable by-product of the increased scientific interest. Thus, the basic laboratory investigation of these exceedingly rare disorders has been advantageous both in clinical medicine and in cell biology.

A major objective of this book is to consider laboratory approaches used in the identification and characterization of genes that predispose to human cancer (and this chapter addresses cytogenetic approaches in particular). It is worth noting, however, that the genes responsible for the disorders under consideration in this particular chapter are not "genes that predispose to cancer" per se, at least as far as is known (just discussed). When homozygous, each of the genes results in a clinically recognizable phenotype, and it is the phenotype rather than the mutant gene itself that predisposes to cancer. The bases for the cancer proneness of the several phenotypes that are the consequence of homozygosity for these rare genes are diverse, and few generaliza-

tions can be made with respect to the reasons that cancer emerges so commonly. Hence, no general "test" exists for genetically determined genomic instability. Nevertheless, each condition holds a great deal of interest for the student of neoplasia, and in one sense or other serves as an experimental model. Broadly, study of the chromosome-breakage syndromes provided the basis for the *chromosome-mutation theory of carcinogenesis* [20], and constituted some of the earliest strong evidence in support of Boveri's 1914 theory that a chromosome change in a cell is responsible for neoplastic transformation. It is for this reason that I have taken the space above to place the several disorders in a conceptual framework. In the following section, concise descriptions of each disorder are presented, after which will be mentioned the more interesting abnormalities that cells from homozygous-affected persons display in the experimental, and sometimes the clinical diagnostic, laboratory.

CLINICAL FEATURES OF THE CHROMOSOME-BREAKAGE SYNDROMES

(The Phenotypes of Affected Homozygotes)

Bloom's syndrome (BS) [21, 22]. Severe growth deficiency both pre- and postnatally is the most consistent prominent feature of BS. With the exception of slight microcephaly and its accompanying distinctive cranial configuration and facies, the body proportions are roughly normal. Additional features, varying in degree and frequency of occurrence, make possible the accurate recognition of affected individuals and distinguish them from other forms of growth deficiency. Included among these features are the following: a sun-sensitive facial erythema; immunodeficiency associated with excessive numbers of upper and lower respiratory tract infections; vomiting and diarrhea during infancy; a somewhat restricted intellectual ability, often shifting the person to the lower average/mildly deficient range; well-demarcated patches of hyper- and hypopigmentation on the skin; a high-pitched, slightly raspy voice; and aspermia accompanied by abnormally small testes in males.

Neoplasia both benign and malignant of many types and sites emerges more often than normal in BS; the carcinomata tend to appear decades earlier than in the general population [23]. In the 132 persons in the Bloom's Syndrome Registry [24], 59 malignant neoplasms have been detected, affecting 42 individuals at a mean age of 24.8: 15 leukemias, 30 carcinomata, and 14 of other types. Although a formal comparison remains to be made, the distribution of types and sites of cancer that have occurred in BS does not appear to be strikingly different from that in the general population [23].

Fanconi's anemia (FA) [25]. FA classically consists of the onset of pancytopenia in a preadolescent child with certain anatomic malformations, most

often anomalies of the thumb and kidney. Although the newborn may appear normal, a degree of both intrauterine and postnatal growth deficiency is common. Microcephaly is characteristic, and intellectual ability frequently is mildly to moderately restricted. A poorly described patchy hyperpigmentation of the skin is characteristic. Unless an earlier sib is affected, the diagnosis of FA usually is not made until signs of a hypoactive bone marrow appear, usually thrombocytopenia or anemia, especially if the characteristic absence or hypoplasia of the thumb is lacking as a signal to the pediatrician. Signs of marrow failure usually appear between ages 6 and 9; however, its appearance sometimes is delayed until adulthood. Without treatment, marrow failure progresses to pancytopenia and death from hemorrhage, infection, or anemia. Anabolic steroids are useful in controlling the marrow hypoplasia, thus prolonging life. In some persons with FA, anatomic defects are absent. Some persons with the FA genetic constitution even fail to develop anemia. For these several reasons, FA often is a difficult diagnosis to make.

Cancer was not considered a complication of FA for the first few decades after the syndrome was described (1927), in fact, not until after 1959 when therapy with anabolic steroids was introduced [23]. Now, however, a clear-cut increase in cancer incidence has been documented. As of 1980, 45 instances of cancer were known [23]. The distribution of types of cancers that had occurred was very different from that in the general population: 22 acute leukemias, 16 primary tumors of the liver, and several carcinomata, often at unusual sites. The leukemias were non-lymphocytic, whereas acute lymphocytic leukemia (ALL) is the commonest leukemia of childhood. In many ways the leukemias that emerge in FA are similar to those that emerge from marrows that have become hypoplastic for perhaps any of several other reasons—the “aplasia leukemia syndrome” [26]. This brings into question the role in FA, if any, played by genetically determined chromosome mutation in cancer onset—the main subject under consideration here.

Ataxia-telangiectasia (AT) [27]. In AT, the onset of a progressively more severe cerebellar ataxia accompanied by telangiectasia of the bulbar conjunctivae and rims of the ears occurs in infancy or early childhood. Absence or anomalous positioning of Purkinje cells in the cerebellum is the basis for the ataxia. Lymphoid tissue throughout the body is poorly developed, the thymus being hypoplastic or absent. Clinically significant immunodeficiency supervenes during late childhood or adolescence; it usually is not present from birth and frequently is completely absent during early childhood. Other clinical features of AT include progeric skin changes, growth deficiency, ovarian dysgenesis, and insulin-resistant diabetes. AT patients exhibit hypersensitivity to therapeutic X-irradiation, lethal outcomes of cancer radiotherapy having been reported.

The types of cancers that occur in AT are well known from the reports of the Immunodeficiency Cancer Registry where, in fact, AT is the major contributor of cancers [28]. Lymphoid malignancy predominates, but carcinomata are increased also, representing a quarter of the AT-associated neoplasms registered [23].

The Nijmegen breakage syndrome (NBS) [29]. The phenotype in this recently recognized disorder is not fully defined but is known to include variable immunodeficiency, developmental delay, and increased cancer susceptibility. Its discovery as a clinical syndrome was unusual: a striking cytogenetic disturbance that appeared identical to that in AT (to be described below) was observed in patients with some of the clinical features of AT—but with neither ataxia nor telangiectasia from which AT gets its name! Microcephaly and a learning restriction sometimes have been present, indicating that some as yet pathologically undefined central nervous system disturbance exists in NBS. Results of somatic cell hybridization studies using radiation-induced inhibition of DNA replication as a marker have demonstrated that AT and NBS are genetically distinct [30]; however, one individual in a complementation group of NBS has been found who shares the clinical features of both AT and NBS, which indicates some relationship.

Xeroderma pigmentosum (XP) [31, 32]. Hypersensitivity to sunlight is the major, often the only, clinical feature in this genetically heterogeneous entity. The severity of the sunlight hypersensitivity varies, extending from nothing more than excessive freckling and a tendency to sunburn, to severely damaged skin, with extensive hyperpigmentation accompanied by solar keratoses, telangiectasia and depigmentation, and innumerable skin cancers. In many persons with XP, the cornea also is affected, resulting in varying degrees of blindness. Some affected persons exhibit growth deficiency, and a minority of persons also manifest central nervous system disease, varying from mild areflexia and hearing loss to severe mental deficiency and deafness. Unless severe neurological deficiency is to be a part of the clinical disease in a given patient, the affected homozygote will appear normal at birth, the freckling and other changes in the skin and cornea to come months to years later. A proportion of affected persons display excessive and protracted hyperemia of the skin and/or photophobia when exposed to the sun, and these may be the earliest symptoms of the disease. The severity of the skin disease, and the eye disease if that also is a clinical feature in a given patient, is roughly proportional to the amount of sun exposure the patient has experienced. Persons with dark complexions in general have less severe skin manifestations.

Integumentary neoplasms of various types, predominantly basal and squamous cell carcinomata and melanoma, generally appear during late childhood or adolescence but sometimes are delayed until adulthood [23]. What about non-integumentary neoplasia? I was surprised to learn when I

surveyed the subject a decade ago [33] that neoplasia in tissues other than that exposed to sunlight seems not to be increased in frequency in XP, with the possible exception of brain tumors. Given the ubiquity of carcinogens in the environment and the fact that XP cells are deficient in repairing not just the damage to DNA that is produced by sunlight but also that produced by many chemicals, increased non-integumentary neoplasia would be expected in persons with XP. More information concerning this puzzling and potentially very informative situation is needed [23, 34].

Werner's syndrome (WS) [35]. Growth deficiency and premature degenerative changes affecting a variety of tissues and organs are the most striking clinical features of WS. The diagnosis is made in adulthood, and death occurs at the mean age of 47. Growth is normal in childhood but ceases in the early adolescent years. Adult heights and weights are somewhat below normal. Characteristic features of WS include a "pinched" facies with a beaked nose due to nasal cartilage hypoplasia; a stocky trunk with a protuberant abdomen; thin, spindly limbs due to muscle wasting; premature greying and thinning of the hair; cataracts that appear between the ages of 20 and 30; a thin, high-pitched voice; scleroderma-like changes, mainly on the face, hands, and feet where skin atrophy is prominent; hyperkeratosis of the soles, where ulceration often occurs and leads to amputation; widespread atherosclerosis; diabetes mellitus; hypogonadism; and osteoporosis.

As of 1983, more than 40 cancers had been reasonably well documented in WS [23]. The distribution of types was clearly different from that affecting the general population, and from that in the other syndromes under consideration here. An excess of tumors affecting connective tissue had occurred, and some of the commonest human cancers had not, notably lung, colon, and stomach carcinomata and those of lymphoid tissue.

LABORATORY DIAGNOSIS OF THE CHROMOSOME-BREAKAGE SYNDROMES

With the exception of NBS and WS, each of the syndromes under consideration here has been subjected to extensive laboratory investigation. BS, FA, AT, and NBS display cytogenetic abnormalities in untreated PHA-stimulated blood lymphocytes; in WS, cultured but otherwise untreated skin fibroblasts display a characteristic cytogenetic abnormality. Table 1 provides an entree to the cytogenetics of this group of disorders. With the exception of WS (which may not have been examined), cells from each syndrome have been demonstrated to manifest abnormal response to a variety of DNA-damaging agents. Variability in response among persons with the same clinical entity is prominent. The variable responses occur at least in part because of the genetic heterogeneity that exists in four of the six entities (already mentioned). Other

TABLE 1. The Main Cytogenetic Evidence of Genomic Instability in the Chromosome-Breakage Syndromes. (Increases in Comparison to Normal are Graded as Follows: 1, Great; 2, Moderate; 3, Mild; 4, Detectable but Slight; —, Not Increased. A Blank Indicates Inadequate or Absent Information.)

Syndrome	Chromatid Lesions in PHA-Stimulated Lymphocytes										Pseudodiploid**					
	SCEs in Cultured Cells*					Micronuclei					In Vivo			In vitro		
	Untreated		Treated with			Un- treated		Treated with			In Vivo		Bone Marrow		LCLs	
	Breaks@	Qr	MC†	UV	Xray	MC	EMS	UV	Mucosae	Bone Marrow	In Vivo	Bone Marrow	Fibroblasts	Low-SCE	High-SCE	Fibro- blasts
BS	2	1	—	—	—	1	1	1	1	3	—	3	2	—	—	1
FA	1	—	1	—	—	—	—	—	2 or —	—	—	3	3	—	—	4
AT	3	—	—	—	1	—	—	—	—	—	—	—	—	—	—	3
NBS	3	—	—	—	1	—	—	—	—	—	—	—	—	—	—	—
XP	—	—	—	4	—	3	—	3 [§]	—	—	—	—	—	—	—	—
WS	—	—	—	—	—	—	—	—	—	—	—	—	—	3	—	1

Abbreviations: EMS, ethyl methanesulfonate; DEB, diepoxybutane; LCL, Epstein-Barr virus-transformed B-lymphoblastoid cell line; MC, micronuclei; PHA, phytohemagglutinin; Qr, a quadriradial configuration of Class I [3b]; SCE, sister-chromatid exchange.

*In medium containing 5-bromodeoxyuridine (BrdU)

**Apparently balanced translocations in complements of 46 chromosomes.

@Gaps, breaks or rearrangements, but exclusive of Class I Qrs.

†MC and several other drugs including cis-platinum compounds, DEB, nitrogen mustard, isoniazide, and Trenimon (the first to be reported).

§Present in only some complementation groups of excision-defective XP.

explanations for the reported variability in response following exposure to DNA-damaging agents and even the variability in the amount of spontaneous chromosome breakage that exists include biases introduced in the experimental design, comparisons with inadequate numbers of normal controls, and inexperience on the part of investigators. Only the most constant laboratory responses that are made by cells from homozygous-affected persons with the disorders under consideration will be mentioned in the following discussion. (Little comment will be made concerning the normal laboratory responses usually made by heterozygotes, who in each instance are normally developed and healthy people.)

Table 2 indicates the tests that are of the greatest value in confirming a diagnosis in patients suspected on clinical grounds of having one of these disorders.

Bloom's syndrome. BS is the only chromosome-breakage syndrome in which one relatively simple laboratory test can be used to rule the diagnosis in or out with certainty. The chromosomes of PHA-stimulated BS blood lymphocytes exhibit excessive numbers of SCEs (sister-chromatid exchanges) when the cells are cultured for two cell-division cycles in BrdU-containing medium. (The question is unanswered as to whether the SCE rate in BS cells is elevated constitutionally or results from hypersensitivity of the cells to BrdU; however, certain evidence suggests that the SCE elevation is constitutional [38].) An elevated SCE frequency also has been detected in BS bone marrow cells in short-term culture and in T-lymphocytes, EBV-transformed B-lymphocytes, and skin fibroblasts in long-term culture. The only BS cells that fail to exhibit SCE elevation are (i) minor populations of lymphocytes circulating in the blood of some affected homozygotes, and (ii) some EBV-transformed lymphoblastoid cell lines (LCLs), presumably derived from such low-SCE B-lymphocytes. These enigmatic low-SCE BS cells are best explained to be the result of somatic mutation, although the locus/loci mutated has not been identified.

In addition to the characteristic SCE elevation, cultured B- and T-lymphocytes and skin fibroblasts from BS patients exhibit increased chromosome instability, manifested by an abnormally great number of chromatid gaps and breaks and structurally rearranged chromosomes [39, 40]. Approximately 1% of PHA-stimulated T-lymphocytes in metaphase display a characteristic type of four-armed configuration (Qr, quadriradial) composed of two homologous chromosomes with opposite arms of the figure of equal length and with the centromeres positioned opposite one another (Fig. 2) [36]. A Qr of the type characteristic of BS indicates that an interchange of DNA had taken place between a chromatid of each member of the homologous chromosome pair during the preceding S phase and that the interchange had occurred at apparently homologous sites. Also commonly found in BS metaphases are

TABLE 2. Useful Laboratory Procedures for Confirming Clinical Diagnoses in the Chromosome-Breakage Syndromes. (1, Confirms the Diagnosis; 2, Strongly Supportive of the Diagnosis). (See Table 1 for Abbreviations.)

Syndrome	Analysis of Blood Lymphocytes for Excessive:				Analysis of Skin Fibroblasts for Excessive:			
	Spontaneous Breakage	Qr Formation	Breakage After MC or DEB	SCE	Numbers of Pseudodiploid Clones	Cytotoxicity to MC	Numbers of Pseudodiploid Clones	Sensitivity to Ionizing Radiation UV Radiation
BS	2	2		1				
FA	2		1			1		1 [37]
AT	2				1			1 [37]
NBS	2				1			1 [12]
XP							1	
WS								

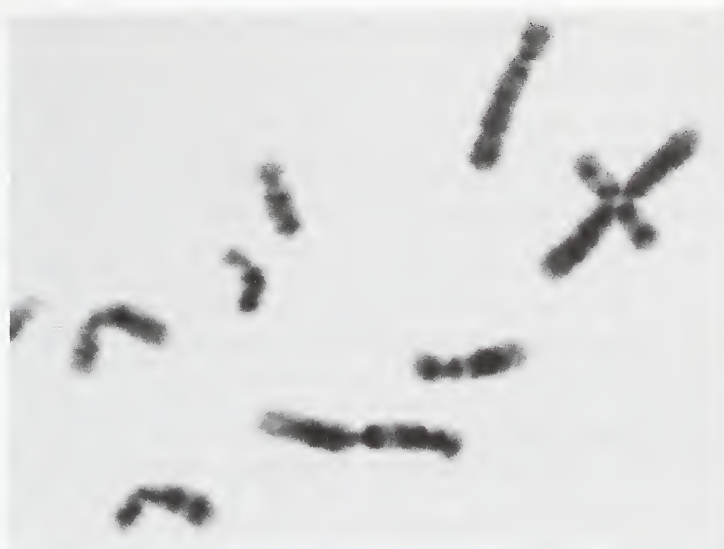


Fig. 2. A quadriradial configuration (Qr) characteristic of BS, in this case involving the two No. 6 chromosomes. (G-banding of metaphase chromosome of a PHA-stimulated blood lymphocyte from an individual with BS.) The Nos. 6 rather than lying separately in the metaphase cell are held together because an exchange had occurred between one chromatid of each, the point of exchange being at or very near the centromere. Depending on the segregation of the chromatids at the anaphase that would follow, homozygosity at all loci distal to the point of exchange is a possibility. Because the HLA locus is on proximal 6p, loss of HLA locus is on proximal 6p, loss of heterozygosity at the HLA locus of the type detected in the mutation assay described in references 3 and 4 could be explained by such a homologous interchange. Qrs of this type are found many times more frequently in BS than in normal cells. They are cytological evidence that somatic crossing-over can occur in human cells.

anomalous unions between sister chromatids of single chromosomes—sister-chromatid “reunions”; in contrast to SCEs and Qrs they presumably would be lethal to the affected cell because of the large deletions of DNA and the dicentric chromosome that would result. Although homologous Qrs and sister-chromatid reunions occasionally are observed in dividing cells from normal, healthy persons, a great increase in their frequency is characteristic uniquely of BS. Neither the SCEs nor the symmetrical interchange configurations (Qrs) are necessarily mutagenic—although the interchanges would give rise to recombined chromosomes in half of the progeny of affected cells; however, the presence of increased numbers of open gaps and breaks and structurally rearranged chromosomes does suggest that the chromatid-

interchange mechanism that is excessively activated in BS cells is highly error-prone.

Excessive numbers of cells with micronuclei exist in buccal mucosal and exfoliated urinary mucosal cells from persons with BS [41]. This finding constitutes important evidence that at least some degree of the dramatic chromosome instability demonstrable in vitro in BS cells exists in vivo. Confirmatory to the increased spontaneous mutability of BS cells in vivo are the results of two studies estimating the frequency of locus-specific mutations that accumulate in tissues of persons with BS. Mutations at the HPRT locus [42] and the GPA locus [43, 44] are greatly increased in number in BS. The results of the (particularly informative) GPA assay surveys demonstrate that not only are an enormous number of mutant cells present in persons with this genetic constitution— $1-3 \times 10^{-3}$ —but that the mutations that exist are of many types, including deletions and somatic recombination. Clearly, homozygosity for the BS mutation determines a mutator phenotype [45]; mutations of many types, arising from base substitutions, deletions, and homologous recombination and presumably affecting all loci, accumulate excessively in populations of BS cells proliferating both in vitro and in vivo.

Fanconi's anemia: The two most striking cytogenetic features of FA [39, 40] are (i) an increased number of chromatid gaps and breaks in PHA-stimulated blood lymphocytes, with a modest increase in interchange configurations formed usually between non-homologous chromosomes, and (ii) an enormously increased number of chromatid breaks and interchanges in essentially every metaphase following exposure of the cells to certain DNA-damaging agents, especially DNA cross-linking agents. The increased chromosome breakage and interchange that is observed in FA occurs at concentrations of chemicals that cause minimal damage in cells from other individuals. (As in BS, where blood lymphocytes lacking the high-SCE phenotype may be found, populations of FA lymphocytes that fail to exhibit excessive breakage following exposure to DNA cross-linking agents are encountered sometimes. Here also the "normal" cells are enigmatic, but again are best explained by somatic mutation.)

Variability has been encountered in experienced laboratories examining the spontaneous chromosome-breakage rate in FA lymphocytes in short-term culture, although usually an increase is easily demonstrable. FA fibroblasts in long-term culture also exhibit increased numbers of chromatid gaps and breaks. However, some studies of metaphases in freshly aspirated bone marrow have reported that no increased chromosome breakage exists there. This raises a scientifically interesting question, the answer to which has relevance to hypotheses made concerning the cause of the proneness to neoplasia of FA homozygotes. Is the high rate of spontaneous chromosome breakage in FA cells the consequence of in vitro cultivation? Correspondingly,

can a cell's environment *in vivo* sometimes become such that chromosome instability is induced? And, is that postulated dangerous *in vivo* environment that can result in instability dependent on exogenous agents only or can it come about spontaneously? Evidence bearing on these questions is scanty: nonmalignant clones of cells with marker translocations are more easily found in the bone marrow and blood of FA patients than normal [39, 40]. In the sole relevant report [46], a study not of *in vivo* chromosome breakage but of locus-specific mutations, increased numbers of FA blood lymphocytes mutant at the HPRT locus were reported to have been found. Whether the increase in HPRT-locus mutations is spontaneous (endogenous) in FA or is the result of cumulated abnormal responses to unidentified environmental agents that the patients must encounter—agents that, like mitomycin C (MMC) and diepoxybutane (DEB), can cause chromatid damage—is unknown. As yet, untreated and uncultured FA cells cannot be said to manifest a mutator phenotype.

The hypersensitive response of FA cells to DEB, nitrogen mustard, isoniazide, and MMC is a useful diagnostic tool. If a hypersensitive response to one or more of these compounds, eg, DEB [47, 48], is demonstrable in an individual having a phenotype compatible with FA, the diagnosis of FA can be considered confirmed. Another valid test for FA, and one more adaptable for use by routine cytogenetics laboratories that might lack experience with FA or that prefer not to handle DEB, measures short-term survival of cells in the presence of MMC, comparing survival in a co-cultivation system comprised of opposite-sexed FA *vs* control cells; the number of Y-bearing metaphases present after several days of incubation are scored [49]. Decreased survival of cells from an individual suspected of having FA in this co-cultivation system lends strong support to the diagnosis, as yet no other genotype having been identified that gives hypersensitivity to MMC.

Ataxia-telangiectasia. The cytogenetics of AT [39, 40, 50] has contributed to concepts concerning mutant clone formation and the evolution of such clones in neoplastic transformation and progression. However, cytogenetics is less useful in the clinical diagnosis of AT than it is in BS and FA. This is partly because the response of AT T-lymphocytes following stimulation with PHA is poor (for unknown reasons) often necessitating that repeated cultures be harvested before adequate numbers of metaphases are available for analysis. If and when enough AT cells can be studied, increased numbers of chromatid lesions characteristically are found. Chromosome instability also is present in AT skin fibroblast cultures, and its demonstration there is often easier than in lymphocytes.

That instability may exist *in vivo* in AT as well as *in vitro* is indicated by the presence in some patients of a 5- to 14-fold increase in the number of exfoliated cells of the oral cavity and urinary tract that contain micronuclei [51, 52]. Some AT heterozygotes also exhibit increased numbers of micronu-

cleated cells [51, 52], pointing to an effect of the AT mutation in single dose, in contrast to the evidence against such for the BS mutation [41]. Locus-specific mutations also are increased in number in vivo: a 7- to 14-fold increase in circulating erythrocytes mutant at the GPA locus [53].

Low LET ionizing radiation and the radiomimetic drug bleomycin produce an inordinately great amount of chromatid breakage and rearrangement in AT cells [50, 54]. Exposure of normal cells to low LET ionizing radiation and bleomycin is followed by an immediate cessation of DNA replication and retardation of progression through the cell-division cycle. Presumably this response constitutes a self-protective mechanism that enhances a cell's chance of repairing radiation-induced damage. The protective mechanism is defective in AT cells. This abnormal feature of AT cells makes it possible to distinguish AT from other neurological disorders that feature ataxia [37]. In fact, an anomalous response to ionizing radiation is seen in cells from only one other reasonably well-defined clinical condition, NBS (below), so that its demonstration usually is sought when the diagnosis AT (or NBS) is being considered.

A cytogenetic finding that is highly characteristic of PHA-stimulated AT blood lymphocytes and that is found only in AT and NBS is the presence of clones of cells recognizable as such because of the presence of specific chromosome rearrangements. It is not unusual to find that a large proportion of metaphase figures from a given patient belong to one or another clone. The chromosome regions affected in these rearrangements are highly characteristic, the breakpoints being at or near one of the three T-cell-receptor loci, which are on chromosome Nos. 7 and 14 (bands 7p13-14, 7q32-35, and 14q11.2) and a region on chromosome No. 14 proximal to the immunoglobulin heavy-chain locus (band 14q32.1) [55-57]. Translocations affecting the T-cell-receptor loci sometimes are found in single cells in cultures of blood lymphocytes from normal persons; however, only in AT (and NBS) are they greatly increased in frequency. The proportion of a given AT patient's dividing blood lymphocytes that are members of pseudodiploid clones varies, both between patients and between blood samples taken at different times from the same patient. In my opinion, the presence of such mutant clones in a significant proportion of dividing blood lymphocytes justifies their being considered benign populations of neoplastic cells [40]. Sometimes the size of the clones with translocations or inversions of chromosome Nos. 7 and 14 fluctuates with time, some clones expanding, others decreasing. In a few instances, clones of AT lymphocytes with chromosome rearrangements affecting the distal locus on 14q apparently have evolved into leukemic populations [58, 59]. We have argued [40, p. 146] that the severe clinical immunodeficiency that eventually appears in AT in a sense is acquired rather than congenital, being the consequence of loss of the normally wide diversity that is necessary in an intact immune system; ie, progressive constriction of the diversity takes place as an inordinate expansion

occurs of just one or a small number of clones of lymphocytes that have obtained a growth advantage through a mechanism completely unrelated to the immune response. The growth advantage presumably would have been acquired through an aberrant chromosome rearrangement(s). By this hypothesis, the age at which clinical immunodeficiency presents itself in any given patient would await (i) the occurrence of a translocation that provides a growth advantage to some lymphocyte lineage, and (ii) the considerable expansion of the abnormal (clonal) lineage, with the concomitant displacement of cells having other immunological specificities.

The Nijmegen breakage syndrome. Cells from NBS exhibit a cytogenetic phenotype indistinguishable from that of AT. Increased numbers of chromatid gaps and breaks are observed, as are clones of lymphocytes with translocations affecting the T-cell receptor loci [29]. The same anomalous response made by AT cells to low LET ionizing radiation is observed in NBS cells [50, 54]. Fusion of normal cells with AT and NBS cells corrects the defective response to such radiation, as does fusion of AT cells with NBS cells. The results of somatic cell hybridization studies demonstrate a striking degree of genetic heterogeneity to exist in both disorders (as already mentioned), at least four complementation groups being present in AT and two in NBS [30].

Xeroderma pigmentosum. The DNA-repair and -replication defectiveness of XP cells has been reviewed in an earlier volume in this series of monographs [12] and will not be described further here. Cells from most XP patients are defective at excision repair, whereas "variant" XP cells are defective at daughter-strand-gap filling. Eight complementation groups of excision-defective XP have been identified.

Cytogenetic examination of XP cells has not been particularly useful as a diagnostic tool although a few abnormalities have been detected. Following UV-irradiation the chromosomes of XP cells from some patients tend to exhibit more gaps and breaks than normal, so that for heuristic purposes XP can be considered a "conditional chromosome-breakage syndrome." Excision-defective XP cells are reported to display a few more SCEs than normal cells even when untreated [60]; XP cells of some but not all complementation groups exhibit more SCEs than do normal cells when both are exposed to similar doses of UV-irradiation [61].

Similarly, however, XP might also be referred to as a "conditional cancer-prone condition," because avoidance of sunlight decreases the risk of skin cancers. Thus, although chromosome instability is not a constitutional feature of XP cells, the neoplasia that emerge with increased frequency in UV-irradiated tissues of affected persons also are not constitutional—it depends on the environment—and very possibly are mediated through microscopically visible chromosome mutation, as is the case with most human cancers. By this hypothesis, cancer in XP is indirectly dependent on sunlight, to produce the

damage to DNA which, when unrepaired or repaired unduly slowly, predisposes to a mutation when the cell replicates its DNA.

Werner's syndrome. Chromatid gaps and breaks seem not to be increased in frequency in WS cells dividing in vitro. The characteristic cytogenetic abnormality of WS is to be found in skin fibroblasts in long-term culture [62-64]. Most WS fibroblast cultures that have been studied have turned out to be clonal, all of the metaphases in a given culture exhibiting the same chromosome translocation. The translocations are different in different cultures. Multiple cultures set up from the same fragment of skin may exhibit different translocations. On rare occasions the same translocation has been found in cultures derived from separate fragments of a skin biopsy, probably indicating that the translocation had existed in vivo. Cultures of EBV-transformed B-lymphocytes also may contain marker translocations [63], although studies of such cells have been few. This striking cytogenetic finding of WS has been termed VTM, variegated translocation mosaicism [62].

The question then is, if chromosomes from cells of WS patients exhibit no more spontaneous breaks and rearrangements than chromosomes in cells from normal persons, why do skin fibroblast cultures derived from biopsies of persons with WS almost invariably develop into lines the cells of which bear chromosome translocations? Fibroblast cultures derived from a normal person's skin sometimes do contain clones with translocations; however, the basis for the extraordinary excess of clones in WS is completely obscure. We [63] have reasoned that because WS skin fibroblast cultures characteristically are difficult to initiate, only a few fibroblasts emerging from an occasional explant in the culture vessel, those WS cells that will grow in vitro have been relieved of some presently unexplained restriction on in vitro proliferation by certain translocations per se. The loci affected in the translocations in WS fibroblast cultures are many; however, if this hypothesis concerning release of a growth restriction via chromosome mutation is correct, analysis of the breakpoints in WS fibroblasts should disclose previously unrecognized genetic determinants of importance in fibroblast-growth regulation. The postulated restriction on growth of WS fibroblasts and its release by chromosome translocation may be relevant to the predisposition of WS patients to connective tissue tumors mentioned above.

CONCLUDING REMARKS, WITH ADDITIONAL RECOMMENDATIONS

Thus, six completely different clinical phenotypes, described above, feature genomic instability that is detectable using standard cytogenetic techniques, in some cases in combination with techniques from radiobiology. In five of the six conditions, both the clinical and the laboratory abnormalities are distinctive. In the sixth (NBS), the pattern of cytogenetic instability and radiosensi-

tivity that exists is identical to that in AT, but the AT and NBS clinical phenotypes are different. In addition to there being six clinically recognizable disorders, genetic heterogeneity figures prominently in four of the six, indicating that an impressively large number of loci of importance for maintaining the integrity of the human genetic material have been identified. The following comments pertain to laboratory detection of these genes, in both homozygotes and heterozygotes.

Diagnosing affected homozygotes. Persons homozygous for each of these rare mutations almost invariably are identified by clinicians after an explanation has been sought for some developmental disturbance or symptom. The laboratory test that is available for confirming the diagnosis of each phenotype (clinical syndrome) goes beyond that done routinely in most diagnostic laboratories, meaning that research-oriented laboratories often are called upon to confirm the clinical diagnoses. Table 2 indicates the tests that are most useful diagnostically in the chromosome-breakage syndromes. In view of the varied phenotypes of the disorders and the fact that the specific laboratory tests most useful in the diagnosis of each disorder are best performed by only a few research laboratories, it is reasonable to suggest that one or two reference laboratories be designated for diagnosing each disorder. Although the burden imposed on these research laboratories would not be great, a central source of funding to offset the extra expense should be established. Doubtless improved and simpler diagnosis of both clinically affected homozygotes and heterozygotes will come with the cloning of the genes that are mutated in the different chromosome-breakage and DNA-repair syndromes. Even then, the idea of just a few designated diagnostic laboratories to which clinicians can turn may be desirable.

For the present, the laboratory tests employed for the diagnosis of BS and FA are fairly definitive. In AT, cytogenetics is not often definitive unless an extensive search for clones of lymphocytes with the characteristic translocations can be carried out. A method for detecting such clones using recombinant techniques, ie, using probes for the characteristic breakpoints found in AT, would be valuable. Also, it might be possible to develop a blood test for the aberrant AT response to ionizing radiation. The laboratory diagnosis of XP at present is also not completely satisfactory, and three needs are identifiable. First, a test for excision-defective XP that could be performed on blood samples (or perhaps on lymphoblastoid cell lines (LCLs) that are so easily established from blood samples) would be invaluable because affected persons exhibiting nothing more than excessive freckling then could be tested. (Severe cases of XP are easily recognized by physicians, but it seems probable that XP is significantly underdiagnosed.) Currently, the taking of a skin biopsy and its development into a fibroblast cell line is a prerequisite for testing for XP, and that is a formidable undertaking for and discouraging to the average physi-

cian. A second need in XP is a relatively straightforward laboratory test that would confirm the diagnosis of variant XP; this diagnosis often is made by default, ie, when cells of a patient who exhibits the clear-cut clinical features of XP prove to be competent at excision repair. Third, an easier system is needed for identifying the complementation group into which a given excision-defective XP patient, once diagnosed, falls. For WS, no diagnostic test is available. In WS, the presence of a translocation in the karyotype of a fibroblast cell line derived from a person with clinical features, and especially the presence of different (unique) translocations in several lines from the same patient, is, as far as I know, found only in WS, so that that laborious approach can be attempted, recognizing at the outset that WS fibroblast cell lines are exceptionally difficult to initiate and handle.

Heterozygote detection. Methods for identifying heterozygotes for these mutations would be useful for those engaged in investigating the biology of the disorders, for population oncologists, and for physicians/geneticists handling families ascertained through an affected homozygote. During the investigations that have disclosed the array of abnormalities in homozygotes for each of these mutations (described above), heterozygotes also have been examined (the observations in NBS and WS being few, however). With the exception of AT, heterozygotes for each condition usually exhibit both a normal clinical phenotype and a normal response in the particular laboratory test characteristically used to identify the homozygote. Some FA heterozygotes have been reported to overrespond to DEB [47], but more studies there are needed. Even in AT the often borderline abnormality detectable in the heterozygote is not diagnostic (ie, slight radiosensitivity or increased breakage, pseudodiploid clones in skin fibroblast cultures, or increased numbers of micronucleated cells in exfoliated epithelium). Molecular techniques will, of course, be useful for heterozygote identification once the genes for each of the disorders are cloned; in the meantime, however, efforts should continue to develop definitive tests to diagnose the carrier states. Especially welcome will be tests that will identify BS, FA, and AT heterozygotes, to facilitate epidemiologic studies aimed at answering the question definitively, Does heterozygosity for any of these mutations predispose to cancer, or to any other morbid condition?

Registries. Registries of persons affected with selected rare and very rare genetic disorders are worthwhile and should be developed and maintained. Registries can be efficient, inexpensive vehicles for learning much about rare conditions in a short time. Unfortunately, adequate financial support for registries of rare genetic disorders has been lacking. Support by agencies that make grants for research in the usual sense have not often been willing to make long-term commitments to the support of registries. This possibly is because registries usually are research resources, rather than research itself.

This situation must be corrected if willing research-oriented groups with proven experience and judgment studying a given condition are to be encouraged to undertake developing and maintaining a registry. Nevertheless, for the chromosome-breakage syndromes, registries have been established: (i) the Bloom's Syndrome Registry was developed in my laboratory in the early 1960s and is maintained in the Laboratory of Human Genetics at The New York Blood Center [24]; (ii) the International Fanconi Anemia Registry was begun in 1982 by Drs. A.D. Auerbach and T.M. Schroeder-Kurth and is maintained in the Laboratory of Investigative Dermatology at The Rockefeller University [65]; (iii) the Xeroderma Pigmentosum Registry was begun in 1981 by Drs. A.D. Andrews, K.H. Kraemer, W.C. Lambert, and me and is maintained in the Department of Pathology at the University of Medicine and Dentistry of New Jersey in Newark [66, 67]; (iv) families affected with AT are followed by Dr. M. Swift in the Department of Medicine at the University of North Carolina [18]; (v) Dr. C.M.R. Weemaes in Nijmegen, The Netherlands [29], gathers information on each of the persons diagnosed with NBS [68]. While the primary aim of registries is to accumulate basic scientific and epidemiologic information, families affected with these rare disorders themselves benefit greatly from there existing one "expert" group that can deal either directly with them or with their physicians and provide up-to-date information about the condition. Contact of an affected family with such an interested and informed group—I should add, with such a group if it is capable of communicating in a useful way with non-experts—can be very helpful in family/patient management. Advice and education can be provided concerning genetic counseling and prenatal diagnosis, long-term follow-up, and new therapies. With respect to cancer, they might, for example, advise a family on a reasonable clinical program of surveillance for the early detection of solid tumors in those in the family that are at increased risk of such; or as another example, on the advisability of bone marrow storage.

Cloning the loci affected. Cloning of the loci that are mutated in the chromosome-breakage and DNA-repair syndromes is a major focus for a number of basic laboratory investigators. Once this is accomplished it will be possible to determine the role played by the several affected (mutant) enzymes in maintenance of the structural integrity of DNA in somatic cells, and thus of cellular homeostasis. Results of these efforts should provide insight into the molecular processes that are involved in the neoplastic transformation and tumor progression that occurs not just in these rare disorders but in the general population—a major reason for studying these rare mutations. Also, as already stated, the cloned loci will facilitate clinical diagnosis: diagnosis of homozygotes, who present clinical disease, and identification of heterozygotes, who phenotypically appear normal.

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CHAPTER 5

Epidemiologic Evidence of Genetic Susceptibility to Cancer

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INTRODUCTION

In their widely quoted report to the Office of Technology Assessment of the U.S. Congress, Doll and Peto [1] calculate that 80% of cancer is environmentally caused and therefore avoidable. Their estimate is based on the difference between the observed cancer rates for white males under age 65 in nine areas of the U.S., and the number that would be expected if instead those areas had the lowest known international incidence rate for each cancer type. Their report has had a profound influence on the conduct of epidemiologic studies during the last decade: epidemiologists have concentrated on studying environmental determinants of cancer and have largely ignored genetic factors and environmental-genetic interactions. Although many risk factors for cancer have been found during the past ten years, the strategy promoted by Doll and Peto of risk factor identification and elimination has not produced the anticipated results in cancer control, leading some to question the strategy [2].

Even if Doll and Peto are correct that 80% of cancers are “environmental,” this does not imply that, at most, 20% are “genetic.” Cancer etiology may be described by the cells of a two by two table with genetics and environment acting as independent determinants (Fig. 1). The distribution of cancer in the various cells of the matrix is not known, but we can construct a rough estimate. The concept that 80% of cancer is environmental and 20% is not environmental may be reflected in the column totals shown at the bottom of Figure 1. As is clear from the construct of the table, these figures in no way influence the row totals, ie, the frequency of genetic determination of cancer. If there were accurate measures for these row totals, we could solve for each cell of the table. Unfortunately such data do not exist. We can, however, provide approximate values for some of the cells, and in this manner estimate the values of the other cells and the row totals.

One cell for which there are reasonable estimates is that of pure genetic cancers, which are thought to constitute 5% of all cancers [3]. Using this value in Figure 1 fixes the rate of “spontaneous” tumors at 15% since the column must add up to 20%. Estimates for pure environmentally determined cancers

		Environment		
		-	+	
Genetics	-	spontaneous 15%	pure environmental 2%	17%
	+	pure genetic 5%	gene- environment interaction 78%	83%
		20%	80%	100%

Figure 1.

do not exist. I would argue that they are rare, probably less than 2% of all cancer. The basis of this argument is that there are essentially no cases in the human cancer literature in which cancer develops in most individuals who were highly exposed to a carcinogen (in the absence of known genetic susceptibility). For example, only 5–10% of lifetime heavy smokers ever develop lung cancer, and only a small fraction of persons occupationally exposed to benzidine or β -naphthylamine ever develop bladder cancer. Using the value of 2% in the pure environment cell fixes the values for the remaining cell and the row totals shown in Figure 1. The result of this analysis is that 78% of cancer falls into the gene-environment interaction cell, and that 83% of cancer has a genetic component. Thus, to Doll and Peto's statement that 80% of cancer is environmental, we can add that 80% of cancer is genetic, and 80% is environmental and genetic.

Figure 1 is not intended to provide precise estimates, but rather is an heuristic tool for understanding the interaction between genetics and environment in cancer etiology. Only a small portion of the population may be genetically susceptible to a particular tumor type or exposure. If this be true,

identifying the genetic basis of susceptibility and understanding gene-environment interactions may be more important from the perspectives of both basic science and public health than identifying new risk factors for disease.

Several approaches have been taken in trying to estimate the importance of genetics in common cancer occurrence. These range from comparisons of cancer rates in populations or ethnic groups, to studies of specific families, to use of molecular genetic probes in direct measurement of the association between genes and cancer. Different sets of assumptions, biases, and pitfalls exist for each approach, and the results require careful interpretation. This chapter briefly reviews the epidemiologic evidence for genetic susceptibility to cancer using comparisons between populations, and families. This is followed by a more detailed review of the epidemiologic issues involved in studies at the molecular level.

POPULATION STUDIES

Migration studies have been used sometimes to explore differences in cancer rates between populations and to determine whether these differences are genetic or environmental in etiology. Such studies must make several critical assumptions: 1) The portion of the population that migrated is similar to the portion that stayed behind in terms of genetics, habits, and exposures. 2) The migrant population retains its genetic similarity to the home population. 3) The migrant population acquires the habits and exposures of the host population. 4) Ascertainment of cancer is equivalent in both populations being compared.

When these assumptions are met, a change in cancer rate observed among a population of migrants may be ascribed to environmental factors. For example, comparisons of cancer rates in Japanese immigrants to Hawaii show striking changes in their risk for various cancers (Table 1). Rates for esophageal and gastric cancer in Japanese immigrants dropped to levels near caucasians in Hawaii, while rates for colorectal and breast cancer rose dramatically. These differences are presumably due to environmental factors.

In contrast, it is hard to argue that a cancer site with unchanged rates is genetically determined: the lack of change in lung cancer rates (Table 1) may be due to immigrants maintaining their same smoking habits, rather than a profound genetic effect. Migration studies of this sort have little power to address directly genetic hypotheses, and should not be used, as they sometimes are, as evidence of lack of genetic effect.

Ethnic Differences

Other types of population comparisons do provide evidence of a genetic role in carcinogenesis. Miller [4] reviewed ethnic differences in cancer incidence

TABLE 1. Annual Cancer Incidence Rates (per 100,000 population) by Site in Japan and of Japanese and Caucasians in Hawaii*

Primary Cancer	Sex	Japan	Hawaii	
			Japanese	Caucasians
Esophagus	M	15 11	4.6	7.5
Stomach	M	133 129	40	22
Colon	M	7.8 8.7	37	37
Rectum	M	9.5 9.0	30	20
Lung	M	24 30	38	96
Prostate	M	1.4 1.3	15	34
Breast	F	34 30	122	187
Cervix	F	33 40	15	24
Corpus uteri	F	3.2 2.0	41	71
Ovary	F	5.1 5.5	16	27

*Adapted from Doll and Peto [1]. Rates in Japan from Miyagi prefecture 1968–71 (upper entry) and Osaka prefecture 1970–71 (lower entry). Hawaiian rates from years 1968–72.

by site, sub-site, and age at diagnosis. The age-incidence curve for testicular cancer has a dramatic peak at 25–29 years in the U.S. white population, but there is no corresponding peak among blacks or Japanese. Similarly, the peak childhood occurrence of acute lymphocytic leukemia that is seen at four years of age in U.S. whites, in Japan, and Great Britain, does not occur in U.S. blacks. Ewing sarcoma is essentially a disease of whites, with non-whites being resistant to the causes of the disease. These ethnic patterns of age-incidence appear to be independent of any environmental influence and suggest a genetic basis for susceptibility to these cancers.

Marked variation in site-specific cancer rates across ethnic groups also can be used as evidence of genetic susceptibility. Often this involves a small region of susceptible tissue in a given organ in a particular ethnic group. Using population-based data from the Surveillance, Epidemiology and End Results (SEER) Program, Miller analyzed site and sub-site cancer incidence for U.S. whites, blacks, Japanese, Chinese, and Filipinos for years 1973–84. Colorectal cancer rates were similar across ethnic groups, although the rank-order by ethnic group changed with different sub-sites. By contrast, U.S. Japanese show a high incidence of gastric cancer in the pyloric antrum (11.78 per

100,000 vs 1.4 for white males, 4.75 for blacks, and 3.36 for Chinese). This finding is similar to that seen in Japan, except that in Japan the incidence of gastric cancer of the midportion of the stomach almost equals that of the antrum. With respect to the esophagus, blacks most often develop squamous cell carcinoma of the middle third, while whites most often develop adenocarcinoma of the lower third. Variation in age-specific incidence and incidence of cancer at particular sub-sites across ethnic groups supports the notion that genetic susceptibility plays a role in neoplasia. However, this cannot be used to provide an accurate measurement of the magnitude of the effect.

Genealogy

Several studies have attempted to determine the size of genetic effects on cancer risk by doing population-based genealogic studies. Using computerized genealogies for Utah's Mormon population, and linking to death certificates, Hill and others [5-7] have compared the observed genetic relationships of cancer cases to the genetic relationships expected through computer simulations, where cases are randomly assigned in the genealogy. They found an excess of cases for certain single cancers, and sets of cancers, among related persons compared with that expected by simulation.

In a population-based genealogic study of over 300,000 Mexican-Americans in Laredo Texas, Weiss et al [8] found a statistically significant, but small, excess of familial cancer when all cancer sites were considered together. Except for breast cancer and perhaps ovarian cancer, there was no excess familial risk at single sites. Limitations in the design of these types of studies may lead to underestimation of familial effect, and so a lack of a strong positive result must be interpreted with caution.

FAMILIAL CANCER

Roughly 50 different forms of cancer have been reported to have a hereditary component [9]. There are well-described cancer families in which elevated cancer risk is inherited in simple Mendelian fashion, (eg, polyposis coli and familial retinoblastoma). There are also cancer family syndromes, such as Li-Fraumeni syndrome [10] and the colon-endometrium cancer family syndrome of Lynch [11]. Purtilo et al [12] describe 240 inherited syndromes in which there is an increased incidence of cancer, some of which are marked (see Chapter 4, by German), but together these only account for a small fraction of the cancer seen in the U.S. population.

One in four Americans will develop cancer in their lifetime. Given this rate, groupings of cancers in families may occur by chance alone. As Mulvihill [13] has observed, the definition of a familial cancer cluster is a functional one that depends on the cancer type, age of onset, number of affected family members

and their relationship. For example, the finding of breast cancer in two of three 80-year-old sisters would not appear familial, given the frequency of this tumor in older women, while the finding of breast cancer in two of three 30-year-old sisters would be strongly suggestive of a familial cancer.

Some population surveys of family cancer rates have been completed. Albano et al [14] obtained family cancer history from 565 consecutive cancer patients at an oncology clinic and showed that 199 families (35%) had more than two first- or second-degree relatives with cancer. Half of patients with cancer have been found to have first-degree relatives with cancer [3, 15]. Although this value appears high, the same has been found in a general population screened for cancer [16]. The lack of difference between cancer patients and the general population could be the result of methodologic bias, but given the high frequency of cancer in the population, it may simply be that there is no difference without subdividing by cancer site.

By looking at specific cancer sites, evidence of familial clusters becomes more apparent. Population and case control studies have shown evidence of family clusters of cancers of the stomach, uterus, nasopharynx, central nervous system, leukemia, and Hodgkin disease [17, 18]. Studies of common cancers, such as those of the breast, colon, and lung have also shown strong evidence of familial aggregation.

Characteristics of Familial and Environmental Cancers

There are marked epidemiologic and biologic differences between familial and spontaneous tumors. For example, in breast cancer the familial form tends to occur in premenopausal women and is associated with a history of early menarche, early age of onset, and bilaterality [19], although these relationships have not held in all studies [20]. Women with familial breast cancer have better survival than non-familial cases, and have certain predominant histologic types [21]. Familial breast cancer does not have the same risk factors as spontaneous breast cancer, such as nulliparity, late first-term pregnancy, low parity, and obesity [19]. Unlike postmenopausal breast cancer, which is more prevalent in the northern U.S., premenopausal breast cancer has an almost uniform incidence across the U.S. [22]. Considering familial relationships as a risk factor is also useful in establishing genetic susceptibility to breast cancer. Women having a blood relative with breast cancer are at increased risk for cancer themselves, and this risk increases with closer relationship: Women having a first-degree relative with breast cancer have a two- to threefold increased risk of breast cancer, and the risk is increased further if the woman has both an affected mother and sister [20, 23].

With common colon cancer (ie, ignoring familial polyposis coli and other rare cancer syndromes), genetic susceptibility to simple polyp formation may

be inherited as an autosomal dominant [24]. Even after excluding persons whose colon tumors arose from some form of polyp, 12 to 26% of common colon tumors may be attributable to heritable factors [19]. These familial tumors often occur as multiple primaries in young persons, and tend to localize in the right and transverse colon. Left-sided lesions, ie, those distal to the splenic flexure, are more prevalent in geographic high incidence areas, and migrants from high- to low-risk areas have shown decreases in left-sided lesions with little change in the incidence of right-sided lesions [19].

The finding of a highly significant familial cancer cluster does not necessarily prove that it is of genetic origin, since families may also share environmental exposures, dietary patterns, and other factors that could account for the cluster. For example, there are familial clusters of mesothelioma caused by common exposure to asbestos [25], and familial leukemia following chronic occupational benzene exposure [26]. Conversely, the lack of high relative risk in a familial cluster does not prove that it is not genetic, since Mendelian genetic diseases can have low relative risks depending on gene frequency [27], and several factors tend to dilute our ability to detect even sizable genetic susceptibility risks [28]. There are a sophisticated array of statistical techniques to help dissect the contribution of environmental and genetic factors in such clusters [29]. Unfortunately, these techniques tend to require that "environment" be treated as a single variable, so often they cannot incorporate multiple risk factors (dose, age at exposure and other epidemiologically important exposure characteristics). Similarly, there are sophisticated epidemiologic methods of dealing with environmental variables, but these tend to treat genetics as a simple dichotomous variable: family history positive or negative.

The interaction of familial factors with environmental exposure may have substantial effects on cancer risk, although this area has received little direct attention in epidemiologic studies. Tokuhata and Lilienfeld [30] studied lung cancer in relation to smoking and family history. They showed that after controlling for family history, smoking alone resulted in a fivefold increase in lung cancer risk. Controlling for smoking, first-degree relatives of lung cancer patients had a fourfold increased risk of lung cancer. When smoking and family relationships were combined, the risk of lung cancer was 14 times higher in smoking persons with a positive family history than among the comparison group of non-smoking persons with a negative family history. There were similar findings in a group of 112 women with lung cancer compared with 224 controls. Non-smokers with a positive family history of lung cancer had an odds ratio (OR) of 5.7, smokers with a negative family history had an OR of 15.1, and smokers with a positive family history had an OR of 30 [31]. The increased risk associated with a positive family history of lung cancer could be mediated by non-genetic factors, eg, smoking itself

clusters in families and passive smoking could account for part of the risk. In the two studies just described, however, both the genetic basis of familial risk and the strong genetic-environment interaction appear to be real.

Segregation Analysis in Familial Cancers

Segregation analysis is a method of determining how a genetic trait is inherited in a family: whether it is dominant or recessive, autosomal or sex-linked. There were problems with early analytical techniques for studying mode of inheritance and segregation in familial clusters. In a study intended to highlight these deficiencies, Lilienfeld [32] showed that the well-known phenomenon of familial clusters of medical school attendance at the University of Buffalo Medical School was consistent with a single gene model. The techniques are considerably more sophisticated now [29], but still suffer the limitation of only being able to pick among competing models under consideration. King [18] has identified five general epidemiologic issues and disease characteristics that complicate the application of segregation analysis:

- 1) A disease may be genetically heterogeneous so that one family suffering from a disease may have a different set of susceptibility genes than another family with the same clinical disease. If such families were pooled to obtain adequate sample size, segregation analysis would no longer be appropriate.
- 2) The way in which families are selected for study can bias which genetic model will best fit the data.
- 3) Not all genetically susceptible family members will develop the disease, reducing the risk estimate associated with a particular allele. Incomplete penetrance of this sort is particularly important where environmental exposures may be required to trigger disease.
- 4) Age of disease onset may differ substantially between susceptible relatives, such that persons carrying a particular gene may still develop the disease after the study is completed.
- 5) Environmentally determined or "spontaneous" cases of the disease may occur in the family, which may weaken the fit of the genetic model and decrease the apparent risk of a particular gene.

Cancer studies of migration, genealogy, and family clusters may identify specific groups who could be usefully examined on a more detailed basis, but they are inherently descriptive in nature and cannot elucidate the mechanistic, biologic details of genetic risk. For that, molecular approaches are required.

MOLECULAR GENETICS

An alternative method of establishing the role of genetic susceptibility in cancer risk is to start at the genotypic or phenotypic level and estimate risk

based on inheritance of specific genes. This molecular approach has been criticized because it could miss important risk factors for disease. Peto [33] advocates the black-box approach to disease etiology, using the rationale that the top-down approach of traditional epidemiologic investigations may not identify all risks for disease, but will not miss any major risk factors. However there are important failures of this method; for example, before the laboratory discovery of HIV, the leading hypothesis for the cause of AIDS based on epidemiologic studies was amyl nitrite use [34]. Although there is continued need for the black-box approach of traditional cancer epidemiology, there is also a need for mechanistic, multidisciplinary, molecular-epidemiologic-genetic studies of cancer etiology.

The molecular approach depends on finding candidate genes, phenotypes, or genetic "markers" that correlate with disease risk. Some of these genes and phenotypes are identified through systematic approaches while others are found serendipitously. The general location of the retinoblastoma tumor suppressor gene was identified by mapping chromosomal deletions in affected members of retinoblastoma families, followed by systematic molecular probing of this chromosomal region [35]. The success of this approach depended on earlier family studies and segregation analysis. The systematic approach is now being applied to known familial cancers such as hereditary renal cell carcinoma, familial Wilms tumor, breast cancer and others, in hope that knowledge of the genes responsible for these familial cancers will help us to understand their more common, non-familial, counterparts.

Other genes that appear to control cancer susceptibility were discovered through chance. The debrisoquine and N-acetylation phenotypic variations described in the chapters by Gonzalez and Weber were discovered because of untoward drug reactions, and the association between phenotype and cancer risk was identified later. The genes responsible for these polymorphisms are now the subject of systematic searches.

Epidemiologic Considerations

Associations between a putative genetic susceptibility locus and cancer risk usually arise first in small laboratory studies using samples of convenience. This may involve samples of one kindred of familial cancer patients, or a comparison of an available group of cancer patients to a group of ostensibly "normal" controls (often staff of the research laboratory). Several biases (eg, occupational exposure, ethnicity, and socioeconomic status differences between patients and controls) can distort the risk estimates of such studies. Larger studies may compare hospitalized cancer patients in one hospital's catchment area with normal blood donors, but again, the controls may not represent the population at risk, and the cancer patients may not represent all such cancer patients, so that there remains a potential for bias. As specific

cancer-susceptibility genes, phenotypes, or markers are identified and characterized, they will need to be validated in large studies using samples representative of the U.S. population.

There have not yet been large population studies of genetic or phenotypic markers of cancer susceptibility. The acetylator polymorphism has received the most study to date. These studies highlight the potential problems of different gene frequencies in different populations, the importance of the interaction between phenotype and environmental exposure in determining risk, and the variability in risk by tumor type. The differences in gene frequency across populations can introduce bias if cases and controls do not come from the same populations. Similarly, without exposure data the risk of a particular phenotype may be obscured. Finally, there may be no phenotypic differences between "all cancers" and controls; specific cancers may have elevated risks associated with one phenotype while other cancers have elevated risk associated with the alternate phenotype (see Chapter 2, by Weber).

Although genetic susceptibility to cancer is often considered without exposure information, both play a role in disease outcome. The ability to detect a measurable increase in cancer risk associated with a particular gene may be enhanced by doing studies within environmentally exposed populations. For example, there is little difference between bladder cancer cases and controls in the frequency of slow acetylator phenotype (67% and 57%, respectively) [36]. However, in the subgroup of cases with an occupational history in the dye-manufacturing industry, 96% of the cases are slow acetylator phenotype. The choice of exposure group is critical and depends on the gene of interest and its role in the carcinogenic pathway: Dye-workers are an appropriate group for the acetylator gene since arylamine dyes are presumably detoxified through the N-acetylation pathway. The failure of the general population of bladder cancer cases, or the subpopulation of smoking exposed cases, to show higher frequencies of slow acetylators demonstrates the need for including both genetics and environmental factors in studies of cancer etiology.

Attributable Fraction

The importance of genetic susceptibility in cancer risk can be gauged in terms of the population attributable fraction. Population attributable fraction may be most clearly defined as:

$$AF = \frac{I_p - I_u}{I_p}$$

where I_p is the incidence rate of the disease in the population, and I_u is the incidence rate in persons unexposed to the measure of interest. In most epidemiologic studies the measure of interest is an occupational exposure or

smoking, but it may also be a particular genotype or phenotype. The AF is usually estimated rather than calculated directly, and can vary substantially from study to study depending on the method and values used in the estimation. In addition, a high AF does not necessarily imply a causal effect and may only reflect an association between the measure of interest and other, unmeasured factors. With these limitations noted, the AF does provide a useful way of assessing the public health importance of genetic factors on cancer risk.

For example, in his provocative but as yet unconfirmed study, Swift [37] estimated the relative risk of breast cancer to be 6.8 among women heterozygous carriers of the ataxia-telangiectasia (AT) allele. In order to translate this value into public health terms, Swift calculated the attributable fraction for the AT gene. Such a calculation critically depends on the frequency of the gene in the population, and this is not well known for AT. Using a population frequency estimate of 1.4%, Swift calculated the attributable fraction as being 7.5%. If correct, this would represent over 10,000 cases of invasive breast cancer in the U.S. per year, showing that even though a gene is at low frequency in the population it can have a sizable health effect.

Linkage Analysis

Genetic markers of disease susceptibility are not necessarily involved in the mechanistic pathway. For example, the increased cancer risk associated with certain ABO blood groups has been substantiated through many studies over the years, although it is doubtful that a blood group has any mechanistic role in carcinogenesis. The principle of linkage analysis is to use an array of polymorphic marker genes that are under no selective pressure to find associations between specific alleles and cancer risk. The marker gene can then be used as an indicator of the chromosomal location of the causal, but as yet unknown, disease-susceptibility gene.

Marker genes are useful in epidemiologic studies as surrogates for the true cancer susceptibility genes. Their validity for such studies depends on how closely linked they are to the true gene. The more closely linked a marker gene is to the true susceptibility gene, the more accurately allelic variants of one may reflect allelic variants of the other, and presumably the risk of disease.

This principle also has been applied in reverse. Rather than using marker genes to predict cancer risk, known risk factors for disease have been used to find new marker genes. For example, the epidemiologic finding of an increased risk of breast cancer in women who have moderate alcohol consumption suggests that the genes associated with alcohol metabolism might be marker genes for some as yet unknown breast cancer susceptibility gene. Using this paradigm, Anderson et al [38] have done linkage analysis of polymorphisms in

the alcohol dehydrogenase gene in breast cancer families. Although their initial results do not show an association, other genes remain to be tested.

A limitation of linkage analysis is that there are a finite number of known marker polymorphisms, so that there may not be a marker gene near a cancer susceptibility gene. In 1985, Elston [39] listed 80 polymorphic markers available for typing using blood, saliva, or urine; divided among 23 chromosomes, these offer scant coverage of the vast expanses of genomic DNA. The introduction of direct DNA analysis using restriction fragment length polymorphisms has expanded the number of available markers, increasing the likelihood that there are marker genes near disease susceptibility genes.

In order to detect any unknown cancer susceptibility gene we need close, uniform, coverage of marker genes throughout the human genome. Linkage analysis can generally detect genes lying within 5 to 10 centimorgans of a marker gene [40]. To achieve this level of resolution would require about 160 equally spaced markers along the human genome [41]. With the advent of GC-clamp denaturing gradient gel electrophoresis, VTR fingerprinting, direct sequencing, and the Human Genome Project, a large number of polymorphic markers will soon be available, making even one centimorgan resolution ultimately possible.

Applying a panel of such marker genes in large population studies of cancer patients, families, and controls could reveal a set of marker genes associated with cancer susceptibility. Detailed molecular analysis in the regions of such markers may lead to the identification of candidate genes for cancer susceptibility, as has occurred in retinoblastoma. It is the direct study of these genes, their function, and their interaction with environmental agents that will allow us to understand the complex interplay of genetics and environment in the neoplastic process.

CONCLUSIONS AND RECOMMENDATIONS

Genetic susceptibility may be a critical factor in public health control of chronic disease. Successful public health programs of disease eradication, eg, the elimination of smallpox, the prevention of dental caries through fluoridation, and the control of poliomyelitis have depended, in part, on a Gaussian distribution of disease susceptibility. Harper [42] suggests that for many chronic diseases susceptibility may be distributed bimodally, with a small genetically susceptible population, and a large resistant population. General public health programs seeking, for example, to modify diet or reduce certain exposures, would have little or no effect on disease incidence because most of the population is already genetically resistant, whereas efforts directed specifically at the susceptible subpopulation could have substantial effects. Successful application of Harper's focused approach relies on our ability to identify

the genetically susceptible population. This, coupled with the scientific importance of understanding the genetic basis of disease susceptibility, is the driving force for investigations in this area. The following would facilitate this goal:

- 1) Establish a population based sample of spontaneous, environmental, and familial tumors with detailed epidemiologic, genetic, clinical, and follow-up data, as well as stored biologic samples of tumor, lymphocytes, granulocytes, hemoglobin, urine, and normal cells.
- 2) Develop a panel of marker polymorphisms with complete coverage of the human genome.
- 3) Encourage multidisciplinary studies of cancer, with collection of epidemiologic, genetic, and clinical information as well as collection and storage of a full complement of biologic samples from all individuals.
- 4) Use multiple molecular/genetic markers and probes in epidemiologic studies of cancer.

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CHAPTER 6

Detection of Cancer Predisposition by Hypervariable Region Analysis

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INTRODUCTION

In recent years considerable progress has been achieved in identifying, isolating and characterizing a class of growth-regulatory genes (oncogenes), which are principal participants in malignant cellular transformation. The types of somatic mutations that "activate" these oncogenes in cancer cells, such as rearrangement/translocation, point mutation and gene amplification, are also now well understood. Therefore, attempts to exploit this information to identify individuals with genetic predisposition to common cancers now seem appropriate.

Several studies have employed restriction fragment length polymorphisms (RFLPs) of oncogenes in population surveys of cancer cases and controls. The restriction endonuclease EcoRI identified an allele of *c-mos* present only in 6 patients with breast cancer and one with leukemia. None of 69 unaffected individuals possessed the allele [1]. An EcoRI allele of the oncogene, *L-myc*, is correlated with metastatic potential of lung cancer [2]. Although such results must be viewed as preliminary, the general approach seems promising.

The HRAS1 locus, which has been pathogenetically implicated in a variety of human tumors, is associated with a variable tandem repeat (VTR, hypervariable region, minisatellite) that is located one kilobase 3' to the gene's polyadenylation signal [3]. Variation in the number of 28 base pair (bp) repeat units that comprise the VTR is responsible for hyperallelism at HRAS1 [3]. As described below, several population genetics surveys have demonstrated that low frequency or rare HRAS1 alleles occur at a disproportionately high rate among cancer patients. Therefore, this locus, and perhaps others linked to VTRs, may have utility in cancer risk prediction.

HYPERVARIABLE MINISATELLITES IN THE HUMAN GENOME

The HRAS1 VTR is one of many, perhaps thousands, of minisatellites dispersed throughout the human genome [4, 5]. These structures consist of the

tandem repetition of a short sequence motif, 14 to 100 bp in length. The tandem arrays can be as few as 3–4 units (100–300 bp), or as many as several hundred units (>20 kb) in length. They occur within or near many genes and gene clusters. Locations upstream (insulin; [6]), within an intron (myoglobin; [7]) or downstream (HRAS1; [3]) have been described. The coding sequences of several genes with tandemly repetitive amino-acid sequences, such as proline-rich protein [8] and involucrin [9], are VTRs.

Neither the origin of these structures, nor the mechanism governing their polymorphic variation, has been determined. A “core consensus” sequence, GGGCAGGTGXG, has been described [4], which is a common part of the repeat unit in a number of minisatellites. More recently, a distinct consensus, GC[A/T]GG[A/T]GG, has been reported [10] that bears a strong resemblance to the prokaryotic activator of homologous recombination, χ (GCTG-GTGG; [11]). These observations underlie the notion that, whatever mechanism is responsible for the generation and/or diversification of VTRs, signal sequences are required and are contained within the repeat unit itself.

The most intuitively attractive mechanism for locus diversification is unequal crossing-over [4, 12]. The occurrence of prokaryotic recombination-promoting signals within VTR repeat units is consistent with such a possibility. As described below, however, genetic and structural evidence from the HRAS1 VTR weigh against this mechanism, perhaps definitively. Replication slippage, multiple crossing-over or gene conversion are the remaining options.

Regardless of the process, new allele generation at some VTR loci is considerable. Jeffreys and his collaborators [12] have demonstrated the relationship directly between the degree of locus heterozygosity and rate of mutation. Loci with rates of heterozygosity in excess of 97% have rates of mutation in excess of 5% per gamete [12]. This rate falls off dramatically as heterozygosity declines below 90%.

POTENTIAL FUNCTIONAL ROLES OF MINISATELLITES

The association of VTRs with genes and gene clusters raises the possibility that these structures play a role in the regulation of gene expression. No direct evidence for such a function, however, has yet been obtained. Several VTRs possess enhancer consensus sequence motifs within the repeat unit [13, 14] and several, including HRAS1, possess a modest enhancer activity in vitro [13, 15]. It is intriguing that most viral enhancer elements require the tandem repetition of their enhancer consensus motifs; however, excessive repetition actually diminishes the positive effect on transcription.

Another potential role for VTRs, as an element of origins of DNA replication, is suggested by two disparate observations. First, the Epstein-Barr virus origin of replication, *oriP*, consists of two required DNA segments: a short

palindrome and, approximately 1 kb away, 30 tandem repeats of a 20 bp repeat unit that is required for binding of the viral DNA maintenance protein, EBNA-1 [16, 17]. In addition, we have described an episode of gene amplification (20- to 50-fold) in which the amplicon is very short, c. 5 kb, and contains the chromosome 10 minisatellite, VTR4.1 [18]. This is persuasive evidence that the VTR is very near, if not within, a replication origin. Since this particular VTR arises from a short interspersed repeat (SINE) present roughly 10,000 times per haploid genome [14], the connection with DNA replication may be relevant. Further characterization of the environment of VTRs, as well as functional tests in origin assays, are now required.

HYPERALLELISM AT THE HRAS1 LOCUS

Southern blot analysis of human leukocyte DNAs has revealed a complex and highly polymorphic HRAS1 locus structure [19–21]. Four common alleles, *a1* (allelic frequency 0.61), *a2* (0.12), *a3* (0.11), *a4* (0.08), account for 92% of the total. The size of the fragments containing the hypervariable region range from 1000 bp (*a1*) to over 2500 bp (*a4*). The other alleles at HRAS1 consist of more than 20 fragments whose frequencies range from 0.02 (*a1.2*) to 0.0006 (nine examples). The VTR fragment size of rare alleles ranges from 850 bp to greater than 3,000 bp, and alleles are distributed uniformly throughout this size interval (Table 1).

HRAS1 ALLELIC FREQUENCIES IN CANCER PATIENTS

Our initial study of over 400 alleles, approximately equally divided among cancer cases and cancer-free controls, demonstrated a statistically significant, threefold excess of rare alleles among cancer patients [19]. Since more than ten cancer types were represented in the study population, sample sizes of individual cancers were too small for the accurate assessment of allelic frequency differences. We have subsequently analyzed approximately 1800 alleles from cases and controls (Table 2) to confirm our original result [20, 21]. Rare alleles are twofold more predominant among cases ($p < 0.001$). Among 14 alleles that were detected only once or twice in the total population, 13 were observed only in cancer patients. Cancers of the breast, urinary bladder and colon, as well as acute leukemias, lymphomas, and melanomas, were highly represented among the group of patients with rare alleles. Once again, however, sample sizes were not generally large enough for statistically significant results among individual tumors. The exception was transitional cell carcinoma of the urinary bladder, in which 16% of 86 patients demonstrated at least one rare allele.

TABLE 1. Allelic Frequencies at HRAS1

Allele	Frequency
a1	0.6094
a2	0.1156
a3	0.1072
a4	0.0797
a1.2	0.0241
a1.1	0.0140
a4.1	0.0062
a3.1	0.0056
a0.1	0.0045
a1.3	0.0039
a1.4	0.0039
*a2.2	0.0039
a5	0.0034
a3.5	0.0034
*a2.01	0.0022
a3.2	0.0022
*a4.2	0.0011
*a1.05	0.0011
*a5.2	0.0011
a2.3	0.0011
*a1.35	0.0011
*a3.3	0.0006
*a4.3	0.0006
*a2.1	0.0006
*a2.015	0.0006
*a2.4	0.0006
*a1.15	0.0006
*a2.02	0.0006
*a3.4	0.0006
*a1.25	0.0006

OTHER SURVEYS OF THE HRAS1 LOCUS IN CANCER CASES AND CONTROLS

Since 1985, eleven studies have appeared in the literature quantitating HRAS1 allelic frequencies in cancer patients and controls, bringing the total number of alleles typed to nearly 4,500 [22–32]. Five reports originated in England or Wales [22–26], two from West Germany [27, 28], two from Italy [29, 30], and one each from France [31] and the USA [32]. Most of these studies analyzed a single cancer; a few, two or three. Total sample sizes range from 200 to 464 alleles. Eight of the 11 studies demonstrated an excess of rare alleles in cancer patients. Perhaps of significance was the fact that the four negative studies detected a low overall frequency of rare alleles ($\leq 5\%$), a result significantly different from that of all other studies, including our own (Table 2). Although the majority of the positive studies did not attain

TABLE 2. Summary of HRAS1 Allele Surveys in Cancer Cases and Controls

	Group	Common Alleles	Rare Alleles
Krontiris et al [21]	Cases	481 (0.88)	69 (0.12)
	Controls	806 (0.95)	42 (0.05)
Other studies [22-32]	Cases	1481 (0.88)	211 (0.12)
	Controls	1325 (0.95)	75 (0.05)

statistical significance, we have pooled the data from all 12 studies for comparison with our own database. This was possible because the four common alleles could be accurately identified by size and allelic frequency across study boundaries. The rare alleles could not be individually assessed across studies; but, since the comparison was based on total rare alleles ("Other" in Table 2), a composite study population could be created and analyzed. The results from the pooled 3100 alleles were virtually identical to the 1400 allele study we conducted (Table 2). Both population samples demonstrated a twofold excess of rare alleles in cases (0.12) vs controls (0.05). For the combined studies, this difference represented a relative risk of cancer for those possessing a rare allele of 2.5. This risk was comparable to that for breast cancer in women with an affected first-degree relative.

HRAS1 FAMILY STUDIES

Further investigation of the HRAS1 population phenomenon has naturally turned to disease-association studies in families with prominent histories of cancer. Linkage studies have shown that HRAS1 is not the primary disease locus for certain forms of familial melanoma [32, 33]; see also Table 3), yet the frequency of rare alleles is increased in such families ([33]; Table 3). Hall et al [34] have also reported increased rare HRAS1 alleles in breast cancer patients, but no linkage to the disease in families demonstrating the apparent segregation of a dominant breast cancer allele. These findings are consistent with several possibilities that can be addressed by further family-based studies. Rare HRAS1 alleles may represent secondary pathogenetic influences. As such, the principal disease locus will determine which individuals are at risk, but HRAS1 may contribute to the certainty and/or severity of onset or to other aspects of the phenotype. It is also possible that HRAS1 is loosely linked to the principal disease locus and that rare HRAS1 alleles are in

TABLE 3. Summary of HRAS1 Association with Familial Melanoma

Families with Rare Alleles/Total Families	No. Alleles	Informative Families	Evidence for Association
5/22 (23%)	7 ^a	3	2

^aTwo rare alleles present in the index case of two families.

disequilibrium with pathogenetic alleles of this second locus. Both of these models are being tested in ongoing family studies, in which the degree of HRAS1 allele-sharing among affected relatives and the correlation of phenotypic differences and HRAS1 allele status are being determined.

An intriguing possibility is that the rate of mutation leading to new (rare) VTR alleles is increased in individuals with cancer and in their families. In this instance rare HRAS1 alleles would be markers for a genome-wide process; and other VTR loci would be assumed to be affected. The rate of heterozygosity of HRAS1 (c. 60%) is probably not sufficiently high to observe new mutations directly, unless this rate is unexpectedly greatly elevated in cancer patients. However, the existence of an elevated mutation rate can be measured easily by typing nuclear families with VTR probes of >97% heterozygosity, where the expected mutation frequency, as discussed above, is 5–10% per gamete. Sufficient power for the detection of a three-to fourfold increase is present in a sample size of 150–200 gametes.

THE GENERATION OF HRAS1 HYPERALLELISM

An understanding of how new (rare) alleles arise at the HRAS1 locus might considerably advance our knowledge of both the process(es) responsible for a significant amount of genetic instability in the human genome, as well as the basis for the association of rare HRAS1 alleles with cancer. The molecular cloning and characterization of an HRAS1 gene associated with the unique VTR allele, *a2.1*, have provided important information in this regard [35, 36].

The *a2.1* VTR is 225 bp, or 8 repeat units, larger than the common allele, *a2*. Five kilobases upstream of the VTR, conforming to the usual structural organization of the HRAS1 gene (Fig. 1), is a noncoding first exon. Upon obtaining a molecular clone of this allele from lymphocyte DNA of a familial melanoma patient, we performed routine restriction mapping, followed by DNA sequencing, which revealed a 6 bp deletion in exon 1. The deletion, designated *d1*, occurred 35 bp from the splice donor site and was of no functional consequence. When we examined genomic DNAs of individuals unrelated to the patient from whom *a2.1* was derived, a very interesting and useful correlation was observed. Using a sensitive probe protection assay, 114 chromosomes were typed for the *d1* marker. The deletion was present in 33 of 35 chromosomes, which also possessed *a2* alleles; none of 79 chromosomes bearing *a1*, *a3* or *a4* were *d1*-positive. Thus, the deletion was in absolute linkage disequilibrium with *a2*; its presence in *a2.1* was strong evidence that this unique allele was derived from an *a2* parent.

Another marker near the promotor-exon 1 region of HRAS1, an XhoI restriction fragment length polymorphism, also has been described in absolute disequilibrium with the four common HRAS1 alleles [ref. 37]; see also Fig. 1.

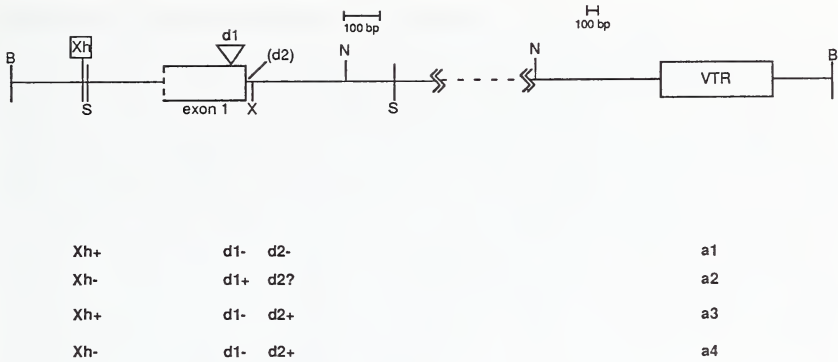


Fig. 1. Haplotypes at HRAS1. An abbreviated restriction map of the HRAS1 locus, highlighting the upstream region containing the promotor and exon 1, as well as the downstream VTR, is depicted. The polymorphic XhoI site (Xh) is boxed and the positions of the d1/d2 markers are indicated. Beneath the map the extended haplotype for each common VTR allele is listed. B, BamHI; S, SacI; X, XmaII; and N, NotI.

During the course of *d1* typing by the probe protection assay, we detected a third region of discontinuity, arbitrarily designated *d2*, which was also in disequilibrium with the downstream VTR. Thus, as shown in Figure 1, these three markers together provided a signature haplotype for each of the common HRAS1 alleles. Given the relationship we established between *a2.1* and *a2*, we decided to type many rare HRAS1 alleles for this upstream haplotype to determine if a pattern of lineage relationships could be discerned. Our result was that 17/17 rare alleles possessed the upstream haplotype characteristic of the common allele nearest in size. For example, *a0.9*, *a0.1*, *a1.1*, *a1.2* and *a1.3* clustered around *a1* and possessed the *a1*-specific haplotype, *XhoI*+*d1*-*d2*-. Similarly, alleles grouped around *a4* possessed the haplotype, *XhoI*-*d1*-*d2*+

The significance of this result was that simple, unequal crossing-over was highly unlikely as the source of new allele generation. Were unequal crossing-over the case, one would have expected the randomization of upstream haplotypes among rare alleles, not the rigid stratification we observed. Rare alleles must, therefore, have emanated from each of the common alleles in an orderly fashion. Double cross-overs, gene conversion or replication slippage must then be considered more likely mechanisms for generating diversity at this minisatellite locus.

DNA SEQUENCE ANALYSIS OF A UNIQUE HRAS1 ALLELE

The 28 bp sequence motif of the HRAS1 VTR showed some sequence variation from repeat unit to repeat unit. This variation was principally

SUMMARY AND RECOMMENDATIONS

Hypervariable minisatellites are genetically unstable structures with no known function. That they might serve as origins of DNA replication or enhancers of transcription is highly plausible. We have shown that the distribution of HRAS1 alleles among cancer cases and controls differs significantly, with rare HRAS1 alleles occurring twice as frequently in cases. This corresponds to a relative risk for cancer of roughly 2.5 for those individuals bearing such alleles. Although the biological basis for this distribution is unknown, our preliminary family studies and those of others suggest that the HRAS1 gene is not the primary disease locus in several families in which breast cancer and melanoma are segregating.

Recommendations for further study:

1) Expansion of allele data for individual tumors types. The relative risk of 2.5 is computed from data representing multiple cancer types. Large studies of individual cancers are now required to determine if heterogeneity among cancer types exists. For example, current data from breast cancer cases suggest that possession of a rare allele will be associated with a significantly higher relative risk than 2.5.

2) Refinement of relative risk for intermediate frequency alleles, a1.1 and a1.2. Because these two alleles could not be discriminated accurately in the studies from other laboratories cited above, they were arbitrarily grouped with rare alleles (Table 2). Our own data, however, indicate that a1.1 and a1.2 are not strongly correlated with affected cases. If they are excluded from risk computations (rare alleles consequently being defined as those with frequencies below 1%; see Table 1), the relative risk increases by nearly an order of magnitude [21]. Therefore, for practical application of allele typing to risk prediction, the lack of association of these "intermediate" frequency alleles must be confirmed through standardization of allele sizing from the various involved laboratories, followed by analysis of pooled data for a1.1 and a1.2.

3) Delineation of interactions with environmental risk factors. This system offers an excellent opportunity to quantitate the interactions of known genetic and environmental components of risk. Such studies will require relatively large sample sizes to attain sufficient power. Cancers of the lung and urinary bladder, and possibly of the breast, should be considered for the initial analyses, since these show particularly strong environmental and VTR associations.

4) Analysis of HRAS1 allele-sharing in family members affected by cancer. As discussed above, the pathogenetic role of rare HRAS1 alleles is best addressed by family studies in which the HRAS1 allele status of affected sibs is determined. The degree to which index cases with rare alleles have affected

sibs with rare alleles will then constitute a measure of HRAS1 linkage to disease. This strategy will detect linkage even where HRAS1 serves as a secondary pathogenetic locus.

5) Determination of VTR Mutation Rates in Cancer Families and Cancer-free Controls. The increase of VTR mutation rates either throughout the genome, or confined to HRAS1, may hypothetically be associated with genetic damage which increases the lifetime risk of cancer. The exceedingly high rate of new allele generation for some VTRs will allow the comparison of mutation rates in families with strongly positive and negative histories of cancer. If differences are documented, the characterization of the genetic locus or loci responsible for this instability will become the major direction of this field.

6) Identification of VTRs associated with other oncogenes. If the HRAS1 VTR plays a role in the pathogenesis of cancer, then VTRs associated with other oncogenes should first be identified, then subjected to the same analysis as HRAS1: the assessment of relative risk associated with single alleles or allelic subsets, followed by family studies.

7) Delineation of the origin and function of VTRs. Understanding the functional and/or structural properties of VTRs will be instrumental in determining whether these regions contribute to pathogenesis or serve secondarily as markers for processes that are responsible for damage to the genome. As an example of the former circumstance, the appearance of new VTR alleles at HRAS1 (and other genes associated with minisatellites) may result in altered enhancer activity. The consequence of such change for control of gene expression and growth regulation is evident. The latter possibility, although formally more difficult to analyze, may lead to the delineation of genotoxic processes intrinsic to the human organism.

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CHAPTER 7

The Use of Comparative Mapping to Identify Loci Involved in Human Carcinogenesis

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The concept of proto-oncogenes is an attractive unifying theory of the genetic component of oncogenesis. Although proto-oncogenes are normal genes thought to be involved in various aspects of cell growth and differentiation, a disruption in their normal regulation is oncogenic. Disruption in regulation of these genes can be caused by mechanisms such as (1) point mutation causing a change in the protein produced, (2) chromosomal rearrangement bringing the gene into the influence of other regulatory loci, (3) amplification of a proto-oncogene, thus producing more of its natural product, and (4) retroviral transfer of an oncogene picked up as part of a proto-oncogene from another cell [1]. A deletion, another type of mutational mechanism, may define an antioncogene, whose presence is regulatory as a suppressor, and whose absence leads to uncontrolled cellular growth [2, 3].

Proto-oncogenes can be classified according to their expression or location in cells: growth factors or growth factor receptors, nuclear or membrane proteins, and so forth [3]. Proto-oncogenes can be active during early growth and differentiation taking on a much lesser effect through regulation of their activity as maturity is reached, but some also express in adult tissue. The general nature and function of proto-oncogenes is still a focus of much research [4].

The theory of proto-oncogenes as major factors in oncogenesis does not necessarily rule out cancers caused by independent environmental effects, and certainly not those caused by genotype-environment interaction [4]. It does provide a starting point to search for genetic effects of cancer.

A genetic etiology is known or implied in many kinds of human cancer. For a few known cases, this causal component ranges from specific genes to multiple factors including genotype-environment interaction [5]. A reasonable hypothesis from the many studies on chemical carcinogens and radiation is that all cancers may be initiated by germinal or somatic mutations [2, 6], and that environmental factors play a role in determining time of onset of

aberrant cellular growth. To identify individuals susceptible to cancer because they carry perturbations of their genome (including mutations, chromosomal rearrangements, retroviral integrations, deletions, fragile sites [7], trisomy, and others) affecting proto-oncogenes, it is necessary to identify the loci involved and the nature of their effects. Mapping studies using restriction fragment polymorphisms and other markers should make it possible to follow putative proto-oncogenes in family studies and help to determine their role in the development of mammalian cancers.

MAPPING AND COMPARATIVE MAPPING

Mapping in mouse and human is progressing at an exponential rate [8–11]. Comparative genomic mapping is progressing just as rapidly in these, the two mammalian species for which there is the most genetic knowledge [9, 12]. In GBASE, the genomic database of the mouse compiled in our laboratory, about 2600 mouse loci, including DNA polymorphisms and other chromosomal markers, are identified. Some 1600 of these are mapped to specific chromosomes. The mouse is an appropriate tool for the study of human genetic diseases for several reasons, chief among which are mouse and human similarities in genome size; in chromosome numbers (human 23 pairs, mouse 20); in embryology; in physiology; and, important to this paper, in immunology and tumor biology. The mouse has significant advantages as a laboratory animal in addition to its short generation time. The study of mouse infectious and genetic disease can thus lead to a better understanding of comparable, even homologous, human conditions.

Several criteria, under the major headings of similarity of molecular gene structure and similarity of biological or biochemical function, have been suggested [12] to assess the homology of human and mouse loci. Loci are homologous if they have been conserved since the evolutionary separation of the two species, about 65 million years ago. At least 45 homologous autosomal segments involving over 350 genes are known to be conserved. The X and Y chromosomes are presumed homologous throughout, except for inversions [13]. In both human and mouse, sites of proto-oncogenes have been mapped, using probes of retroviral sequences [3]. The rapid increase in comparative mapping is mainly due to the use of molecular probes [12].

It is possible, through detailed mapping studies of the mouse and comparative mapping with humans, to aid in identifying human genetic sites of proto-oncogenes. Table 1 gives a list of presently known proto-oncogenes or cancer-related genes in the mouse. It shows the gene symbol, gene name, chromosomal location if known, and recent references concerning mapping of

these genes. For an introduction into earlier literature, one may consult the work of M.C. Green [14].

The loci included in Table 1 are viral and other cancer-related genes, based on the classification of Kozak [15, 16]. They include the endogenous mouse mammary tumor viruses (the *Mtv* loci), endogenous ecotropic murine leukemia viruses (the *Akv*, *Emv*, and *Mov* loci and others), the endogenous non-ecotropic murine leukemia viral genes (the *Mmv*, *Pol*, *Xmmv*, *Xmv* loci), and genes controlling virus replication, viral and tumor specific antigens, and resistance to virus-induced disease. Loci having cancer-related effects but not mentioned by Kozak [16] were identified in a search of GBASE, the genomic data base of the mouse compiled in our laboratory [17]. In addition, we have included the interesting teratoma locus (*ter*), at present unmapped, which disrupts normal growth, causing cells to revert to a more developmentally potent state. Further information on these loci can be found in Green [14] and the references cited in the tables. Not included are over 100 new provirus loci recently reported by Stoye et al [18].

There are 349 cancer-related genes, including endogenous viruses, out of approximately 2600 loci presently known in the mouse. This fraction is in part a consequence of the high fraction of known loci involved in cellular growth and differentiation. It is perhaps also biased by the results of recent intense scientific interest in viral and cancer-related genes.

The map in Figure 1 shows proto-oncogenes, viral loci and other potentially cancer-related genes along with those genes known to be homologous between mouse and human. Table 2 shows the 66 known homologies between human and mouse proto-oncogenes or cancer-related genes. From the number already ascertained, there is an apparent emphasis of work to determine comparative homologies of this group of loci. As further restriction fragment mapping continues in both mouse and human, we can expect major advances in mapping genes. The use of physical mapping, yeast artificial chromosomes (YACS), and pulsed-field electrophoresis will be important tools to advance mapping. An example of a new technique is the study of the frequent length variation in dinucleotide (CA) repeats found throughout the genome [149]. Although we cannot expect these repeats to be homologous between the species they can contribute to mapping nearby genes that may be utilized in comparative mapping.

CONCLUSION

Mapping and comparative mapping in mouse and human are progressing at exponential rates. Significant in this effort is the work to delineate and map loci involved in cancer in both species. If the map position of a locus is known in the mouse, a good prediction often can be made of the map position of the

homologous human locus, due to the significant number and size of genome segments conserved since the evolutionary separation of the two species. The effort to identify flanking markers, both DNA fragments and other polymorphic loci, can then be focused in the suggested area of the human genome. These markers can then be used to follow a putative oncogene in human families, either for research purposes or for genetic counseling.

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TABLE 1. Proto-oncogenes and Other Cancer-Related Genes in the Mouse

Symbol	Name	Chr.	Refs.
<i>Abl</i>	Abelson murine leukemia oncogene	2	***, 19
<i>Abll</i>	Abelson related gene	1	16, 20
<i>Actx</i>	melanoma X-actin	UN	21
<i>Ahi-1</i>	Abelson helper integration site	10	16, 22
<i>Akv-1</i>	AKR leukemia virus inducer-1	7	***
<i>Akv-2</i>	AKR leukemia virus inducer-2	16	***
<i>Akv-3</i>	AKR leukemia virus inducer-3	2	***, 23
<i>Akv-4</i>	AKR leukemia virus inducer-4	11	***, 24
<i>Akvp</i>	AKR leukemia virus protein inducer	UN	14
<i>Araf</i>	raf-related oncogene	X	***, 25, 26
<i>Av-1</i>	Abelson virus susceptibility-1	UN	14
<i>Av-2</i>	Abelson virus susceptibility-2	UN	14
<i>Bas</i>	BALB murine sarcoma oncogene (may = <i>Hras</i>)	UN	27
<i>Bbv</i>	B10.BR/SgLi endogenous ecotropic virus	11	***
<i>Bcl-2</i>	B-cell leukemia/lymphoma-2	1	***, 28
<i>Bcm-1</i>	B cell membrane protein 1	1	28
<i>Bdv-1</i>	BALB/c defective provirus-1	UN	14
<i>Bv-1</i>	C57BL/10 endogenous ecotropic virus	8	***
<i>Bxv-1</i>	B10 xenotropic virus-1	1	***
<i>C58v-1</i>	C58 endogenous ecotropic virus-1	8	***, 29
<i>C58v-2</i>	C58 endogenous ecotropic virus-2	UN	14
<i>C58v-3</i>	C58 endogenous ecotropic virus-3	4	14
<i>C58v-4</i>	C58 endogenous ecotropic virus-4	7	***
<i>Cbl-1</i>	virally transduced oncogene-1	6	30
<i>Cbl-2</i>	virally transduced oncogene-2	9	30
<i>Csfg</i>	colony stimulating factor, granulocyte	11	16, 31
<i>Csfgm</i>	colony stimulating factor, granulocyte macrophage specific	11	***, 24, 31-33
<i>Csfn</i>	colony stimulating factor, macrophage	3	34, 35
<i>Csfmr</i>	colony stimulating factor 1 receptor	18	16, 31
<i>Cv-1</i>	BALB/c virus inducibility	5	***, 36, 37
<i>Cxv-1</i>	C xenotropic virus-1	17	14, 15
<i>Cxv-2</i>	C xenotropic virus-2	4	***
<i>d</i>	dilute (= <i>Emv-3</i>)	9	14, 38-42
<i>Dsi-1</i>	David Steffen integration-1	4	***, 64
<i>Egf</i>	epidermal growth factor	3	28, 35
<i>Emv-4</i>	endogenous ecotropic MuLV-4	UN	14
<i>Emv-5</i>	endogenous ecotropic MuLV-5	UN	14
<i>Emv-6</i>	endogenous ecotropic MuLV-6	UN	14
<i>Emv-7</i>	endogenous ecotropic MuLV-7	UN	14
<i>Emv-8</i>	endogenous ecotropic MuLV-8	UN	14
<i>Emv-9</i>	endogenous ecotropic MuLV-9	1	14
<i>Emv-15</i>	endogenous ecotropic MuLV-15 (A ^y -assoc.)	2	***, 23, 43
<i>Emv-16</i>	endogenous ecotropic MuLV-16	1	***
<i>Emv-17</i>	endogenous ecotropic MuLV-17	1	***, 39

TABLE 1. (Continued)

Symbol	Name	Chr.	Refs.
<i>Emv-18</i>	endogenous ecotropic MuLV-18	9	***
<i>Emv-19</i>	endogenous ecotropic MuLV-19	3	44
<i>Emv-20</i>	endogenous ecotropic MuLV-20	1	45
<i>Emv-21</i>	endogenous ecotropic MuLV-21	18	45
<i>Emv-23</i>	endogenous ecotropic MuLV-23	7	45, 46
<i>Emv-24</i>	endogenous ecotropic MuLV-24	5	45
<i>Emv-25</i>	endogenous ecotropic MuLV-25	10	45
<i>Emv-27</i>	endogenous ecotropic MuLV-27	3	45
<i>Emv-28</i>	endogenous ecotropic MuLV-28	11	45
<i>Emv-29</i>	endogenous ecotropic MuLV-29	8	45
<i>Erba</i>	avian erythroblastosis oncogene A	11	***, 24, 31
<i>Erbb</i>	avian erythroblastosis oncogene B	11	***, 24, 31, 47
<i>Erbb-2</i>	avian erythroblastosis oncogene B-2	11	16, 24, 31
<i>Ets-1</i>	E26 avian leukemia oncogene-1, 5' domain	9	***
<i>Ets-2</i>	E26 avian leukemia oncogene-2, 3' domain	16	***, 48-50
<i>Evi-1</i>	ecotropic viral integration site-1	3	16, 28, 34, 35, 51
<i>Evi-2</i>	ecotropic viral integration site-2	11	16, 24, 31, 52
<i>Fes</i>	feline sarcoma oncogene	7	***, 53, 98
<i>Fgv-1</i>	C3H/Fg virus-1	7	***
<i>Fgv-2</i>	C3H/Fg virus-2	UN	14
<i>Fhe</i>	Friend helper virus erythroblastosis susceptibility	UN	14
<i>Fim-1</i>	Friend MuLV integration site-1	13	16, 54
<i>Fim-2</i>	Friend MuLV integration site-2 integration site-2 (overlaps <i>Csfmr</i>)	18	54
<i>Fim-3</i>	Friend MuLV integration site-3	3	16, 34, 54
<i>Fis-1</i>	Friend virus integration site-1	7	***
<i>Fos</i>	FBJ osteosarcoma oncogene	12	***, 55, 56
<i>Fv-1</i>	Friend virus susceptibility-1	4	***, 52
<i>Fv-2</i>	Friend virus susceptibility-2	9	***, 57
<i>Fv-3</i>	Friend virus susceptibility-3	UN	14
<i>Fv-4</i>	Friend virus susceptibility-4	12	***
<i>Fv-6</i>	Friend virus susceptibility-6	5	14
<i>Gin-1</i>	Gross passage A viral integration region-1	19	15, 16, 58
<i>Gv-1</i>	Gross virus antigen-1	UN	14
<i>Gv-2</i>	Gross virus antigen-2	7	***
<i>Hcs</i>	hepatocarcinogenesis susceptibility	UN	59
<i>Hras-1</i>	Harvey rat sarcoma virus oncogene	7	***, 98
<i>Hsp84-1</i>	Tumor specific transplantation antigen related to heat shock protein 84-1 (= <i>Hsp-1</i>)	7	15, 16, 60, 148
<i>Hsp84-2</i>	... heat shock protein 84-2 (= <i>Hsp-2</i>)	2	15, 16, 60
<i>Hsp84-3</i>	... heat shock protein 84-3 (= <i>Hsp-3</i>)	12	15, 16, 60
<i>Hsp86-1</i>	... heat shock protein 86-1 (= <i>Hsp-4</i>)	12	16, 61
<i>Hsp86-2</i>	... heat shock protein 86-2 (= <i>Hsp-5</i>)	11	16, 61

TABLE 1. (Continued)

Symbol	Name	Chr.	Refs.
<i>Hsp86-3</i>	... heat shock protein 86-3 (= <i>Hsp-6</i>)	3	16, 61
<i>If-1</i>	NDV-induced circulating interferon	3	***
<i>If-2</i>	MTV-induced circulating interferon	UN	14
<i>Ifa</i>	interferon alpha gene family (leukocyte)	4	***, 62-64
<i>Ifb</i>	interferon beta (fibroblast)	4	***, 65
<i>Ifg</i>	interferon gamma	10	***
<i>Ifgr</i>	interferon gamma receptor	10	***
<i>Ifrc</i>	interferon receptor	16	***
<i>Ifx</i>	NDV-induced circulating interferon	X	***
<i>Il-1a</i>	interleukin-1 alpha	2	16, 23, 66, 150
<i>Il-1b</i>	interleukin-1 beta	2	16, 66
<i>Il-2</i>	interleukin-2	3	16, 67, 68
<i>Il-3</i>	interleukin-3 (contained in <i>Csfmu</i>)	11	16, 25, 31, 33, 47, 67
<i>Il-4</i>	interleukin-4	11	16, 67, 70, 71
<i>Il-5</i>	interleukin-5	11	16, 70, 71
<i>Il-6</i>	interleukin-6	5	16, 79, 72
<i>Inha</i>	inhibin-alpha	1	16, 73
<i>Inhba</i>	inhibin-beta-A	13	16, 73
<i>Inhbb</i>	inhibin-beta-B	1	16, 73
<i>Int-1</i>	mammary tumor integration site-1	15	***, 74
<i>Int-2</i>	mammary tumor integration site-2	7	***
<i>Int-3</i>	mammary tumor integration site-3	17	***, 31
<i>Int-4</i>	mammary tumor integration site-4	11	12
<i>Jun</i>	Jun oncogene	UN	64, 75, 76
<i>Junb</i>	Jun-B oncogene	UN	75, 76
<i>Jund</i>	Jun-D oncogene	UN	76
<i>Kit</i>	kit oncogene	5	16, 77-79
<i>Kras-2</i>	Kirsten rat sarcoma oncogene-2, expressed	6	***80
<i>Lck</i>	lymphocyte protein tyrosine kinase	4	***, 23, 62-64
<i>Lif</i>	leukemia inhibitory factor	UN	81
<i>Lmyc-1</i>	lung carcinoma myc-related oncogene-1	4	64, 82
<i>*Lmyc-2</i>	lung carcinoma myc-related oncogene-2	12	82
<i>Met</i>	met proto-oncogene	6	16, 63
<i>Mgsa</i>	melanoma growth stimulatory activity	5	83
<i>Mlv-1</i>	murine leukemia virus-1	UN	14
<i>Mlvi-1</i>	Moloney-MuLV integration site-1	15	14, 15, 74, 84
<i>Mlvi-2</i>	Moloney-MuLV integration site-2	15	***, 74, 84
<i>Mlvi-3</i>	Moloney-MuLV integration site-3	UN	14
<i>Mmv-1</i>	MCF endogenous virus-1	5	***
<i>Mmv-2</i>	MCF endogenous virus-2	3	***
<i>Mmv-3</i>	MCF endogenous virus-3	7	***
<i>Mmv-4</i>	MCF endogenous virus-4	7	***
<i>Mmv-5</i>	MCF endogenous virus-5	1	***
<i>Mmv-6</i>	MCF endogenous virus-6	12	***

TABLE 1. (Continued)

Symbol	Name	Chr.	Refs.
<i>Mmv-7</i>	MCF endogenous virus-7	12	***
<i>Mmv-8</i>	MCF endogenous virus-8	11	14
<i>Mmv-9</i>	MCF endogenous virus-9	1	***
<i>Mmv-10</i>	MCF endogenous virus-10	1	***
<i>Mmv-11</i>	MCF endogenous virus-11	11	14
<i>Mmv-12</i>	MCF endogenous virus-12	3	***
<i>Mmv-13</i>	MCF endogenous virus-13	11	14
<i>Mos</i>	Moloney sarcoma oncogene	4	***, 19, 64, 65, 85
<i>Mov-1</i>	Moloney leukemia virus-1	6	***
<i>Mov-2</i>	Moloney leukemia virus-2	UN	14
<i>Mov-3</i>	Moloney leukemia virus-3	UN	14
<i>Mov-4</i>	Moloney leukemia virus-4	UN	14
<i>Mov-5</i>	Moloney leukemia virus-5	UN	14
<i>Mov-6</i>	Moloney leukemia virus-6	UN	14
<i>Mov-7</i>	Moloney leukemia virus-7	1	***
<i>Mov-8</i>	Moloney leukemia virus-8	UN	14
<i>Mov-9</i>	Moloney leukemia virus-9	11	***, 31
<i>Mov-10</i>	Moloney leukemia virus-10	3	***
<i>Mov-11</i>	Moloney leukemia virus-11	UN	14
<i>Mov-12</i>	Moloney leukemia virus-12	UN	14
<i>Mov-13</i>	Moloney leukemia virus-13	11	***, 86
<i>Mov-14</i>	Moloney leukemia virus-14	X	***
<i>Mov-15</i>	Moloney leukemia virus-15	XY	***
<i>Mov-24</i>	Moloney leukemia virus-24	Y	***, 86
<i>Mov-34</i>	Moloney leukemia virus-34	UN	14, 86
<i>*Mpmv-1</i>	modified polytropic murine virus-1	7	52
<i>*Mpmv-4</i>	modified polytropic murine virus-4	11	52
<i>*Mpmv-13</i>	modified polytropic murine virus-13	5	52
<i>*Mpmv-23</i>	modified polytropic murine virus-23	5	52
<i>Mtv-1</i>	mammary tumor virus locus-1	7	***, 52, 87
<i>Mtv-2</i>	mammary tumor virus locus-2	18	***, 87
<i>Mtv-3</i>	mammary tumor virus locus-3	11	***, 70, 87
<i>Mtv-4</i>	mammary tumor virus locus-4	UN	14, 87
<i>Mtv-5</i>	mammary tumor virus locus-5	UN	14, 87
<i>Mtv-6</i>	mammary tumor virus locus-6	16	***, 87
<i>Mtv-7</i>	mammary tumor virus locus-7	1	***, 88, 89
<i>Mtv-8</i>	mammary tumor virus locus-8	6	***, 87
<i>Mtv-9</i>	mammary tumor virus locus-9	12	***, 55, 87
<i>Mtv-11</i>	mammary tumor virus locus-11	14	***, 87, 90
<i>Mtv-13</i>	mammary tumor virus locus-13	4	***, 89, 90
<i>Mtv-14</i>	mammary tumor virus locus-14	6	14, 87
<i>Mtv-17</i>	mammary tumor virus locus-17	***	87
<i>Mtv-20</i>	mammary tumor virus locus-20	4	14, 87
<i>Mtv-21</i>	mammary tumor virus locus-21	8	***, 87
<i>Mtv-22</i>	mammary tumor virus locus-22	UN	14, 87
<i>Mtv-23</i>	mammary tumor virus locus-23	UN	14, 87
<i>Mtv-24</i>	mammary tumor virus locus-24	UN	14, 87
<i>Mtv-25</i>	mammary tumor virus locus-25	UN	14, 87

TABLE 1. (Continued)

Symbol	Name	Chr.	Refs.
<i>Mtv-26</i>	mammary tumor virus locus-26	UN	91
<i>Mtvr-1</i>	mammary tumor virus receptor-1	16	***
<i>Mxv-1</i>	MA/My xenotropic MuLV-1	UN	14
<i>Myb</i>	myeloblastosis oncogene	10	*** 92, 93
<i>Myc</i>	myelocytomatosis oncogene	15	***, 74, 94-96
<i>Nfxv-1</i>	NFS/N xenotropic virus-1	UN	14
<i>Ngfa</i>	nerve growth factor, alpha	7	***
<i>Ngfb</i>	nerve growth factor, beta	3	***, 28, 35, 51, 97
<i>Ngfg</i>	nerve growth factor, gamma	7	***, 98
<i>Nmyc-1</i>	neuroblastoma myc-related oncogene-1	12	82
<i>Nmyc-2</i>	neuroblastoma myc-related oncogene-2	5	82
<i>Nras</i>	neuroblastoma ras oncogene	3	***, 35, 51
<i>Nras-ps</i>	neuroblastoma ras oncogene pseudogene	14	99
<i>Nxv-1</i>	NZB/BINJ xenotropic MuLV	UN	100
<i>Nxv-2</i>	NZB/BINJ xenotropic MuLV	UN	100
<i>Nzv-1</i>	NZB virus-1	UN	14
<i>Nzv-2</i>	NZB virus-2	UN	14
<i>Pad-1</i>	MMTV LTR integration site	11	31
<i>Pas-1</i>	pulmonary adenoma susceptibility-1	UN	14
<i>Pas-2</i>	pulmonary adenoma susceptibility-2	UN	14
<i>Pas-3</i>	pulmonary adenoma susceptibility-3	UN	14
<i>Pim-1</i>	proviral integration, MCF-1	17	***, 52, 101
<i>Pim-2</i>	proviral integration, MCF-2	6	52
<i>Pol-6</i>	viral polymerase gene-6	8	15, 16, 102
<i>Pol-7</i>	viral polymerase gene-7	12	15, 16
<i>Pol-20</i>	viral polymerase gene-20	5	15, 16
<i>Pol-23</i>	viral polymerase gene-23	2	15, 16
<i>ptr</i>	pulmonary tumor resistance	UN	103
<i>Ptv-1</i>	polytropic virus-1	UN	14
<i>Pvt-1</i>	plasmacytoma variant translocation-1	15	14, 15, 74, 84
<i>Raf-1</i>	murine sarcoma 3611 oncogene-1	6	***
<i>Ram-1</i>	replication of amphotropic virus-1	8	***
<i>Rb-1</i>	retinoblastoma-1	16	104
<i>Rcs-1</i>	reticular cell sarcoma suppression-1	UN	14
<i>Rec-1</i>	ecotropic MuLV receptor-1	5	***
<i>Rec-2</i>	ecotropic MuLV M813 receptor	2	16, 105
<i>Rel</i>	reticuloendotheliosis oncogene	11	***, 24, 31
<i>**Rfv-1</i>	recovery from Friend virus-1	17	***
<i>**Rfv-2</i>	recovery from Friend virus-2	17	***
<i>**Rfv-3</i>	recovery from Friend virus-3	UN	14
<i>Rgv-1</i>	resistance to Gross virus-1	17	***
<i>Rgv-2</i>	resistance to Gross virus-2	UN	14
<i>Rhv-1</i>	resistance to hepatitis virus-1	UN	106
<i>Ril-1</i>	radiation-induced leukemia sensitivity-1	15	***, 107
<i>Ril-2</i>	radiation-induced leukemia sensitivity-2	4	107
<i>Ril-3</i>	radiation-induced leukemia sensitivity-3	1	107
<i>Rmc-1</i>	receptor for MCF virus-1	1	***
<i>Rmcf</i>	resistance to MCF virus	5	***, 52

TABLE 1. (Continued)

Symbol	Name	Chr.	Refs.
<i>**Rmv-1</i>	resistance to Moloney virus	17	***
<i>**Rmv-2</i>	resistance to Moloney virus-2	17	***
<i>**Rmv-3</i>	resistance to Moloney virus-3	17	14, 15
<i>Rras</i>	Harvey rat sarcoma oncogene, subgroup R	7	***
<i>Rrs</i>	resistance to Rous sarcoma	17	14
<i>Rrv-1</i>	resistance to RadLV-1	17	***
<i>Rtp</i>	resistance to transplantable plasmacy- toma MPC-11	UN	108
<i>Rv-1</i>	Rauscher leukemia virus susceptibility-1	UN	109
<i>**Rv-2</i>	Rauscher leukemia virus susceptibility-2	9	14
<i>Rv-3</i>	Rauscher leukemia virus susceptibility-3	X	14
<i>Rvil-1</i>	radiation-induced leukemia virus susceptibility	2	***
<i>Sfpi-1</i>	SFFV proviral integration-1	UN	110
<i>Sis</i>	simian sarcoma oncogene	15	***, 74, 94, 95
<i>Src</i>	Rous sarcoma oncogene	2	***, 23, 43
<i>Srch</i>	Src-homologous sequence	2	14
<i>Sxv</i>	susceptibility to xenotropic virus	1	***
<i>ter</i>	teratoma	UN	14
<i>*Tgfb-1</i>	transforming growth factor, beta	7	15, 16, 111
<i>*Tgfb-2</i>	tumor growth factor, beta-2	1	16, 112
<i>*Tgfb-3</i>	tumor growth factor, beta-3	12	16
<i>Tla</i>	thymus leukemia antigen	17	***, 101, 113
<i>Tnfa</i>	tumor necrosis factor, alpha	17	***, 114
<i>Tnfb</i>	Tumor necrosis factor, beta (lymphotoxin)	17	***
<i>Tra-1</i>	tumor rejection antigen gp96	10	16, 115
<i>Trp53</i>	transformation-related protein 53	11	***, 24, 31
<i>Trp53-ps</i>	transformation-related protein 53, pseudogene	14	15, 16
<i>Xmmv-2</i>	xenotropic-MCF leukemia virus-2	9	***, 41, 52
<i>Xmmv-3</i>	xenotropic-MCF leukemia virus-3	UN	14, 15, 52
<i>Xmmv-5</i>	xenotropic-MCF leukemia virus-5	5	14
<i>Xmmv-6</i>	xenotropic-MCF leukemia virus-6	1	***
<i>Xmmv-7</i>	xenotropic-MCF leukemia virus-7	UN	14, 52
<i>Xmmv-8</i>	xenotropic-MCF leukemia virus-8	4	***
<i>Xmmv-9</i>	xenotropic-MCF leukemia virus-9	1	***
<i>Xmmv-15</i>	xenotropic-MCF leukemia virus-15	7	***
<i>Xmmv-21</i>	xenotropic-MCF leukemia virus-21	12	***
<i>Xmmv-22</i>	xenotropic-MCF leukemia virus-22	3	***, 116
<i>Xmmv-23</i>	xenotropic-MCF leukemia virus-23	4	***
<i>Xmmv-25</i>	xenotropic-MCF leukemia virus-25	12	14
<i>Xmmv-27</i>	xenotropic-MCF leukemia virus-27	6	***
<i>Xmmv-29</i>	xenotropic-MCF leukemia virus-29	8	***
<i>Xmmv-31</i>	xenotropic-MCF leukemia virus-31	7	14
<i>Xmmv-34</i>	xenotropic-MCF leukemia virus-34	12	***

TABLE 1. (Continued)

Symbol	Name	Chr.	Refs.
<i>Xmmv-35</i>	xenotropic-MCF leukemia virus-35	7	***
<i>Xmmv-36</i>	xenotropic-MCF leukemia virus-36	1	***
<i>Xmmv-42</i>	xenotropic-MCF leukemia virus-42	19	***, 117
<i>Xmmv-43</i>	xenotropic-MCF leukemia virus-43	UN	14
<i>Xmmv-44</i>	xenotropic-MCF leukemia virus-44	UN	14
<i>Xmmv-45</i>	xenotropic-MCF leukemia virus-45	UN	14
<i>Xmmv-46</i>	xenotropic-MCF leukemia virus-46	UN	14
<i>Xmmv-47</i>	xenotropic-MCF leukemia virus-47	UN	14
<i>Xmmv-48</i>	xenotropic-MCF leukemia virus-48	UN	14
<i>Xmmv-49</i>	xenotropic-MCF leukemia virus-49	UN	14
<i>Xmmv-50</i>	xenotropic-MCF leukemia virus-50	12	***
<i>Xmmv-51</i>	xenotropic-MCF leukemia virus-51	UN	14
<i>Xmmv-52</i>	xenotropic-MCF leukemia virus-52	5	***
<i>Xmmv-53</i>	xenotropic-MCF leukemia virus-53	UN	14
<i>Xmmv-54</i>	xenotropic-MCF leukemia virus-54	UN	14, 52
<i>Xmmv-55</i>	xenotropic-MCF leukemia virus-55	15	***
<i>Xmmv-56</i>	xenotropic-MCF leukemia virus-56	UN	14
<i>Xmmv-57</i>	xenotropic-MCF leukemia virus-57	UN	14
<i>Xmmv-58</i>	xenotropic-MCF leukemia virus-58	UN	14
<i>Xmmv-59</i>	xenotropic-MCF leukemia virus-59	UN	14
<i>Xmmv-60</i>	xenotropic-MCF leukemia virus-60	UN	14
<i>Xmmv-61</i>	xenotropic-MCF leukemia virus-61	1	***
<i>Xmmv-62</i>	xenotropic-MCF leukemia virus-62	4	***
<i>Xmmv-63</i>	xenotropic-MCF leukemia virus-63	UN	14
<i>Xmmv-64</i>	xenotropic-MCF leukemia virus-64	UN	14
<i>Xmmv-65</i>	xenotropic-MCF leukemia virus-65	3	14
<i>Xmmv-66</i>	xenotropic-MCF leukemia virus-66	UN	14
<i>Xmmv-67</i>	xenotropic-MCF leukemia virus-67	UN	14
<i>Xmmv-68</i>	xenotropic-MCF leukemia virus-68	UN	14
<i>Xmmv-69</i>	xenotropic-MCF leukemia virus-69	UN	14
<i>Xmmv-70</i>	xenotropic-MCF leukemia virus-70	UN	14
<i>Xmmv-71</i>	xenotropic-MCF leukemia virus-71	2	***
<i>Xmmv-72</i>	xenotropic-MCF leukemia virus-72	15	***
<i>Xmmv-73</i>	xenotropic-MCF leukemia virus-73	7	14
<i>Xmmv-74</i>	xenotropic-MCF leukemia virus-74	1	***
<i>Xmmv-75</i>	xenotropic-MCF leukemia virus-75	15	118
<i>Xmmv-76</i>	xenotropic-MCF leukemia virus-76	7	14, 16
<i>Xmmv-Y</i>	xenotropic-MCF leukemia virus-Y	Y	15, 16
<i>Xmv-1</i>	xenotropic murine leukemia virus-1	4	***
<i>Xmv-2</i>	xenotropic murine leukemia virus-2	4	***
<i>Xmv-3</i>	xenotropic murine leukemia virus-3	16	***
<i>Xmv-4</i>	xenotropic murine leukemia virus-4	11	14, 16
<i>Xmv-5</i>	xenotropic murine leukemia virus-5	11	14
<i>Xmv-6</i>	xenotropic murine leukemia virus-6	UN	52
<i>Xmv-7</i>	xenotropic murine leukemia virus-7	Y	16, 52
<i>Xmv-8</i>	xenotropic murine leukemia virus-8	4	16, 52
<i>Xmv-9</i>	xenotropic murine leukemia virus-9	4	16, 52

TABLE 1. (Continued)

Symbol	Name	Chr.	Refs.
<i>Xmv-10</i>	xenotropic murine leukemia virus-10	2	16, 52
<i>Xmv-11</i>	xenotropic murine leukemia virus-11	Y	16, 52
<i>Xmv-12</i>	xenotropic murine leukemia virus-12	8	52
<i>Xmv-13</i>	xenotropic murine leukemia virus-13	13	16, 52
<i>Xmv-14</i>	xenotropic murine leukemia virus-14	4	16, 52
<i>Xmv-15</i>	xenotropic murine leukemia virus-15	9	16, 52
<i>Xmv-16</i>	xenotropic murine leukemia virus-16	9	16, 52
<i>Xmv-17</i>	xenotropic murine leukemia virus-17	5	16, 52
<i>Xmv-18</i>	xenotropic murine leukemia virus-18	19	16, 52
<i>Xmv-19</i>	xenotropic murine leukemia virus-19	14	16, 52
<i>Xmv-20</i>	xenotropic murine leukemia virus-20	11	16, 52
<i>Xmv-21</i>	xenotropic murine leukemia virus-21	1	16, 52
<i>Xmv-22</i>	xenotropic murine leukemia virus-22	UN	52
<i>Xmv-23</i>	xenotropic murine leukemia virus-23	UN	52
<i>Xmv-24</i>	xenotropic murine leukemia virus-24	UN	52
<i>Xmv-25</i>	xenotropic murine leukemia virus-25	9	16, 52
<i>Xmv-26</i>	xenotropic murine leukemia virus-26	8	151, 52
<i>Xmv-27</i>	xenotropic murine leukemia virus-27	13	16, 52
<i>Xmv-28</i>	xenotropic murine leukemia virus-28	5	16, 52
<i>Xmv-29</i>	xenotropic murine leukemia virus-29	UN	52
<i>Xmv-30</i>	xenotropic murine leukemia virus-30	7	16, 52
<i>Xmv-31</i>	xenotropic murine leukemia virus-31	UN	52
<i>Xmv-32</i>	xenotropic murine leukemia virus-32	1	16, 52
<i>Xmv-33</i>	xenotropic murine leukemia virus-33	7	16, 52
<i>Xmv-34</i>	xenotropic murine leukemia virus-34	5	16, 52
<i>Xmv-35</i>	xenotropic murine leukemia virus-35	16	16, 52
<i>Xmv-36</i>	xenotropic murine leukemia virus-36	17	16, 52
<i>Xmv-37</i>	xenotropic murine leukemia virus-37	15	16, 52
<i>Xmv-38</i>	xenotropic murine leukemia virus-38	UN	52
<i>Xmv-39</i>	xenotropic murine leukemia virus-39	UN	52
<i>Xmv-40</i>	xenotropic murine leukemia virus-40	Y	16, 52
<i>Xmv-41</i>	xenotropic murine leukemia virus-41	1	52
<i>Xmv-42</i>	xenotropic murine leukemia virus-42	11	16, 52
<i>Xmv-43</i>	xenotropic murine leukemia virus-43	1	52
<i>Xmv-44</i>	xenotropic murine leukemia virus-44	4	16, 52
<i>Xmv-45</i>	xenotropic murine leukemia virus-45	5	16

*Loci not yet placed on current map.

**Loci not on map until data are reexamined.

***References 14, 15, 16.

TABLE 2. Known Human and Mouse Homologies of Cancer-related Loci

Human		Mouse		Refs.
Chromosomal Location	Locus Name	Chr.	Locus Name	
1p35-p32	LCK	4	<i>Lck</i>	119
1p32	MYCL	4	<i>Lmyc-1</i>	82
1p22.1 or p13	NGFB	3	<i>Ngfb</i>	120
1p22 or p13	NRAS	3	<i>Nras</i>	99
1q21-q32	ABLL	1	<i>Abll</i>	20
1q41	TGFB2	1	<i>Tgfb-2</i>	121
2p24	MYCN	12	<i>Nmyc-1</i>	82
2p13-cen	REL	11	<i>Rel</i>	122
2cen-q13	INHBB	1	<i>Inhbb</i>	73
2q12-q21	IL1A	2	<i>Il-1a</i>	66
2q13-q21	IL1B	2	<i>Il-1b</i>	66
2q33-qter	INHA	1	<i>Inha</i>	73
3p25	RAF1	6	<i>Raf-1</i>	123
3q27	FIM3	3	<i>Fim-3</i>	54
4q11-q12	KIT	5	<i>Kit</i>	77
4q12-q13	MGSA	5	<i>Mgsa</i>	83
4q25	EGF	3	<i>Egf</i>	124
4q26-q27	IL2	3	<i>Il-2</i>	68
5p14-p13	MLVI2	15	<i>Mlvi-2</i>	74
5q23-q31	CSF2	11	<i>Csfgm</i>	125
5q23-q31	IL3	11	<i>Il-3</i>	126
5q23.3-q31	IL5	11	<i>Il-5</i>	71
5q31	IL4	11	<i>Il-4</i>	71
5q33	FIM2	18	<i>Fim-2</i>	54
5q33.1	CSF1	3	<i>Csfm</i>	34
5q33.2-q33.3	CSF1R	18	<i>Csfmr</i>	127
6p23	FIM1	13	<i>Fim-1</i>	54
6p21.3	TNFA	17	<i>Tnfa</i>	128
6p21.3	TNFB	17	<i>Tnfb</i>	128
6p21	PIM	17	<i>Pim-1</i>	129
6q16-q22	IFNGR1	10	<i>Ifgr</i>	130
6q22-q23	MYB	10	<i>Myb</i>	131
7p15-p14	INHBA	13	<i>Inhba</i>	73

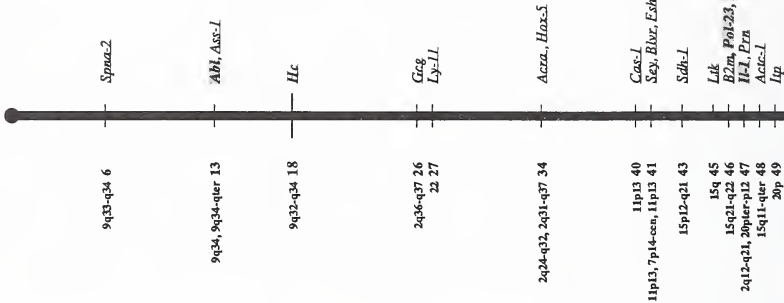
TABLE 2. (Continued)

Human		Mouse		Refs.
Chromosomal Location	Locus Name	Chr.	Locus Name	
7p14-p12	EGFR	11	<i>ErbB</i>	132
7q31	MET	6	<i>Met</i>	133
8q11 or q22	MOS	4	<i>Mos</i>	134
8q24	MYC	15	<i>Myc</i>	135
8q24	PVT1	15	<i>Pvt-1</i>	96
9p22-p13	IFNA	4	<i>Ifa</i>	136
9p22	IFNB	4	<i>Ifb</i>	137
9q34.1-q34.3	ABL	2	<i>Abl</i>	138
11p15.5	HRAS1	7	<i>Hras-1</i>	131
11q13	INT2	7	<i>Int-2</i>	135
11q23	CBL	9	<i>Cbl-2</i>	30
11q23.3	ETS1	9	<i>Ets-1</i>	139
11	BVIX	5	<i>Cv-1</i>	140
12p12.1	KRAS2	6	<i>Kras-2</i>	131
12q12-q13	INT1	15	<i>Int-1</i>	135
12q24.1	IFNG	10	<i>Ifg</i>	141
13q14	RB1	14	<i>Rb-1</i>	142
14q24.3-q31	FOS	12	<i>Fos</i>	143
15q25-q26	FES	7	<i>Fes</i>	144
17p13	TP53	11	<i>Trp53</i>	132
17q11-q12	ERBB2	11	<i>ErbB-2</i>	31
17q11-q21	ERBA	11	<i>Erba</i>	132
17q11-q22	CSF3	11	<i>Csfg</i>	24
17q21-q22	INT4	11	<i>Int-4</i>	31
18q21.3	BCL2	1	<i>Bcl-2</i>	145
19q13.1-q13.2	TGFB	7	<i>Tgfb</i>	111
19	NGFG	7	<i>Ngfg</i>	37
19	RRAS	7	<i>Rras</i>	138
20q12-q13	SRC	2	<i>Src</i>	131
21q21-qter	IFNAR	16	<i>Ifrc</i>	146
21q22.3	ETS2	16	<i>Ets-2</i>	48
22q12.3-q13.1	PDGFB	15	<i>Sis</i>	135
Xp21-q11	ARAF1	X	<i>Araf</i>	147

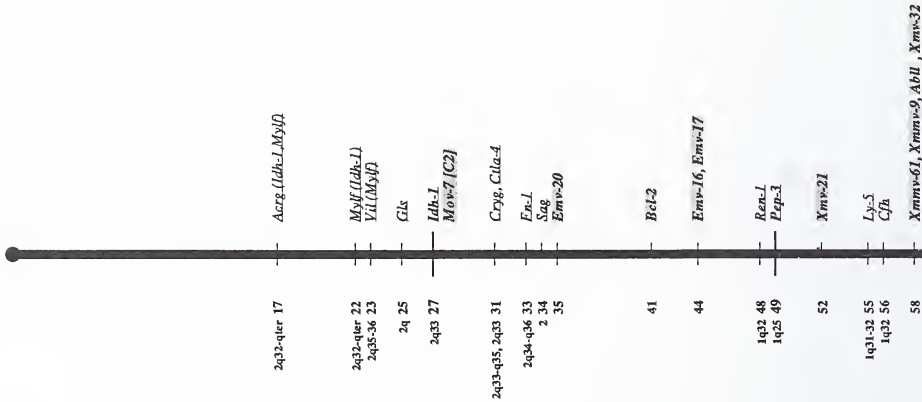
The map in Figure 1 shows proto-oncogenes, viral loci and other potentially cancer-related genes along with those genes known to be homologous between mouse and human. Solid vertical bars represent the chromosomes. Chromosome numbers are shown at the top. Locus symbols are given at the right of the chromosome bars. Hatched symbols are oncogenes or viral related loci. When a second locus symbol is in parenthesis after a first symbol, only the distance from the second locus is known; the direction is not. Numbers to the immediate left of the chromosomes are recombination percentages, giving distances from the centromere in centiMorgans (cM). A gene listed at the bottom of a chromosome has been assigned to that chromosome by parasexual methods; its position on the chromosome is unknown. Relative certainty of a locus position is shown by the length of its respective line through the chromosome: a longer line indicates greater certainty. When many loci are designated to one point, some may be listed on the next line down with a caret indicating they belong to the line above. Numbers in square brackets following a locus symbol indicate the chromosome band location. The numbers to the far left of the chromosome indicate human chromosomal locations for those loci known to be homologous with the mouse. Although the human locus symbol is not given, the respective symbol for the mouse homolog is underlined. Many of the homologous loci are actually proto-oncogenes or cancer-related loci, and they are listed in Table 2.

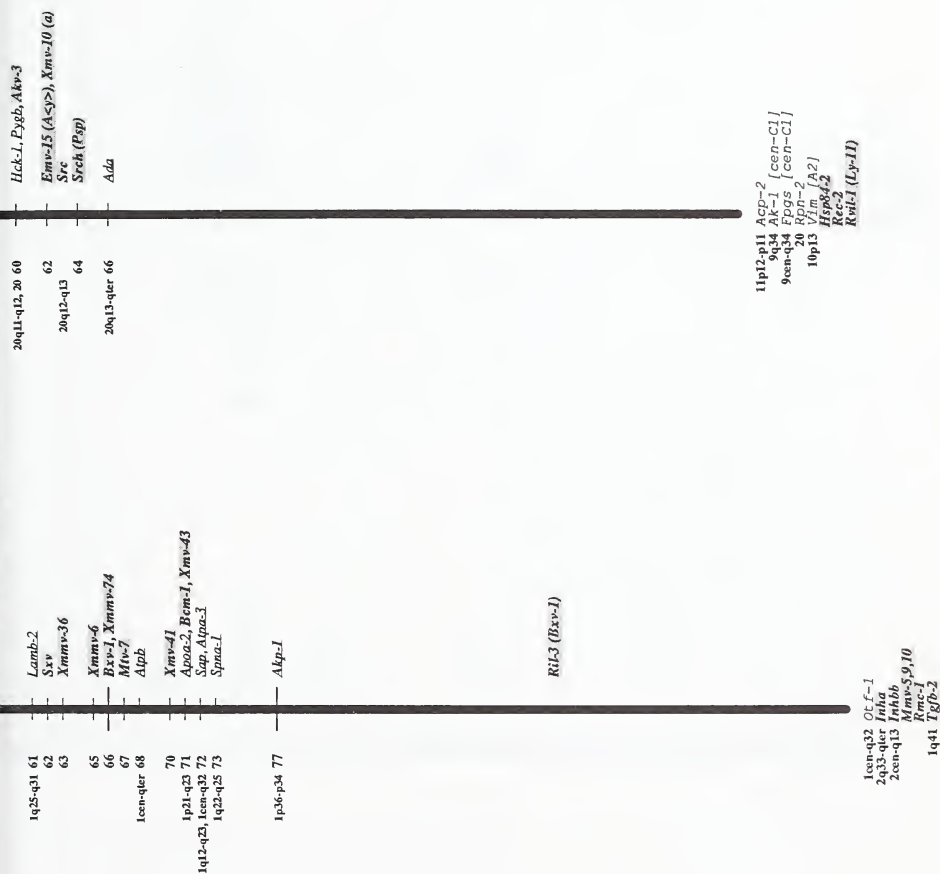
From the locations of cancer-related genes in the mouse genome, one can predict, in many instances, the chromosomal location of homologous loci in the human genome. For example, mouse chromosome 1 is known to encompass only two chromosomal segments from the human genome, the long arm of human chromosome 2 proximally, and the long arm of human chromosome 1 distally. Therefore, the human homolog of mouse *Bcl* (B-cell leukemia, lymphoma-2) can be expected to be found on the long arm of either human chromosome 1, or human chromosome 2. As *Bcl* lies between the mouse chromosome 1 segments known to be homologous to these two human chromosomes, *Bcl* may occur on either.

Chromosome 2

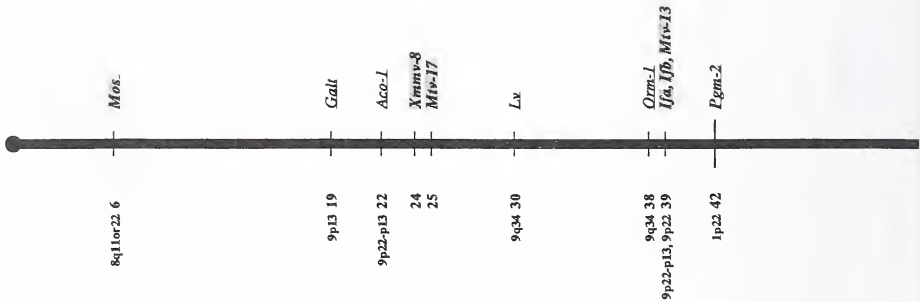


Chromosome 1





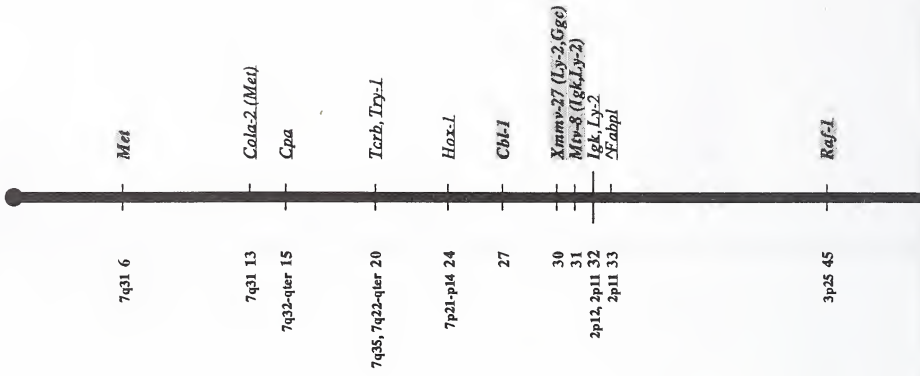
Chromosome 4



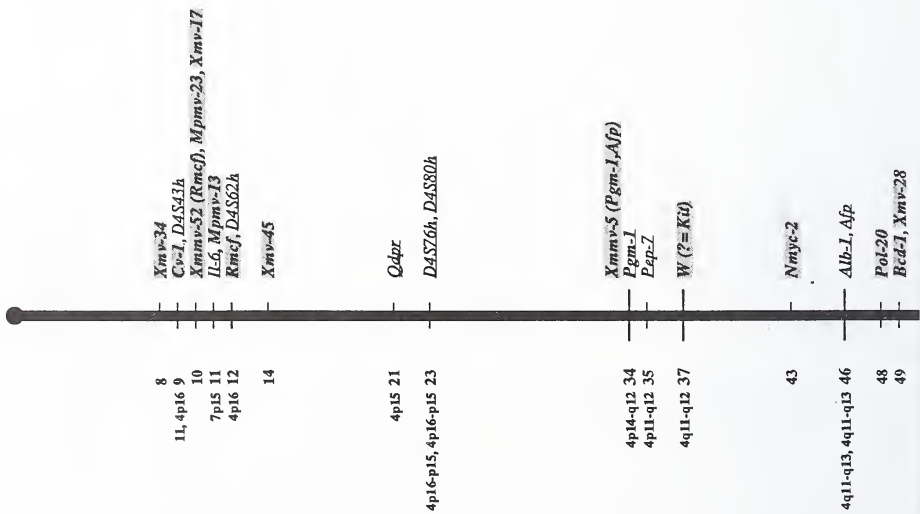
Chromosome 3

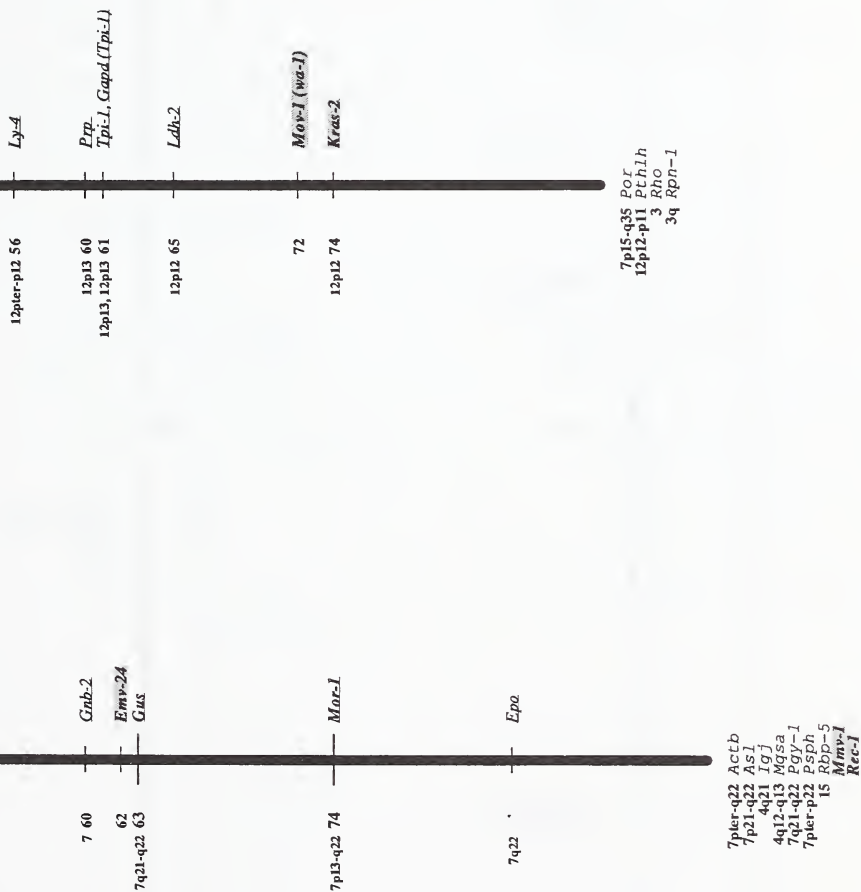


Chromosome 6

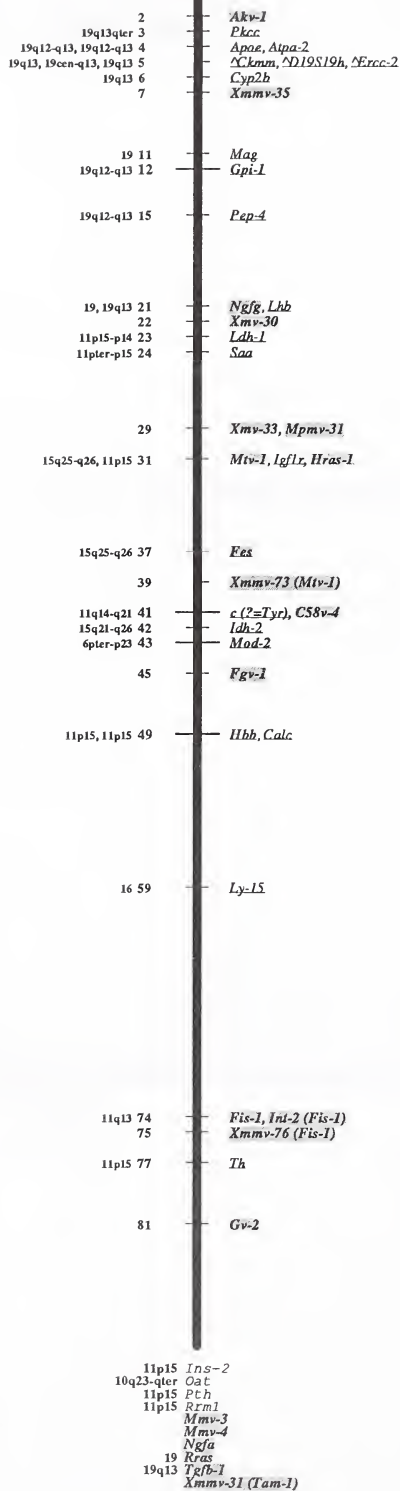


Chromosome 5

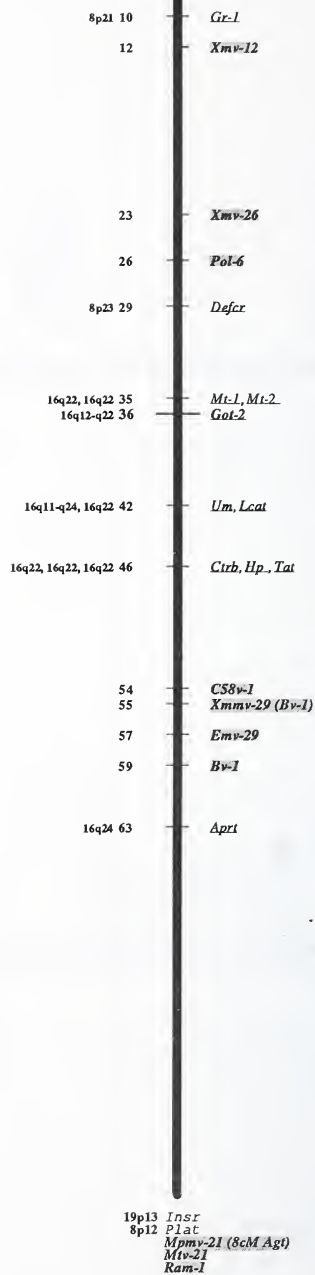


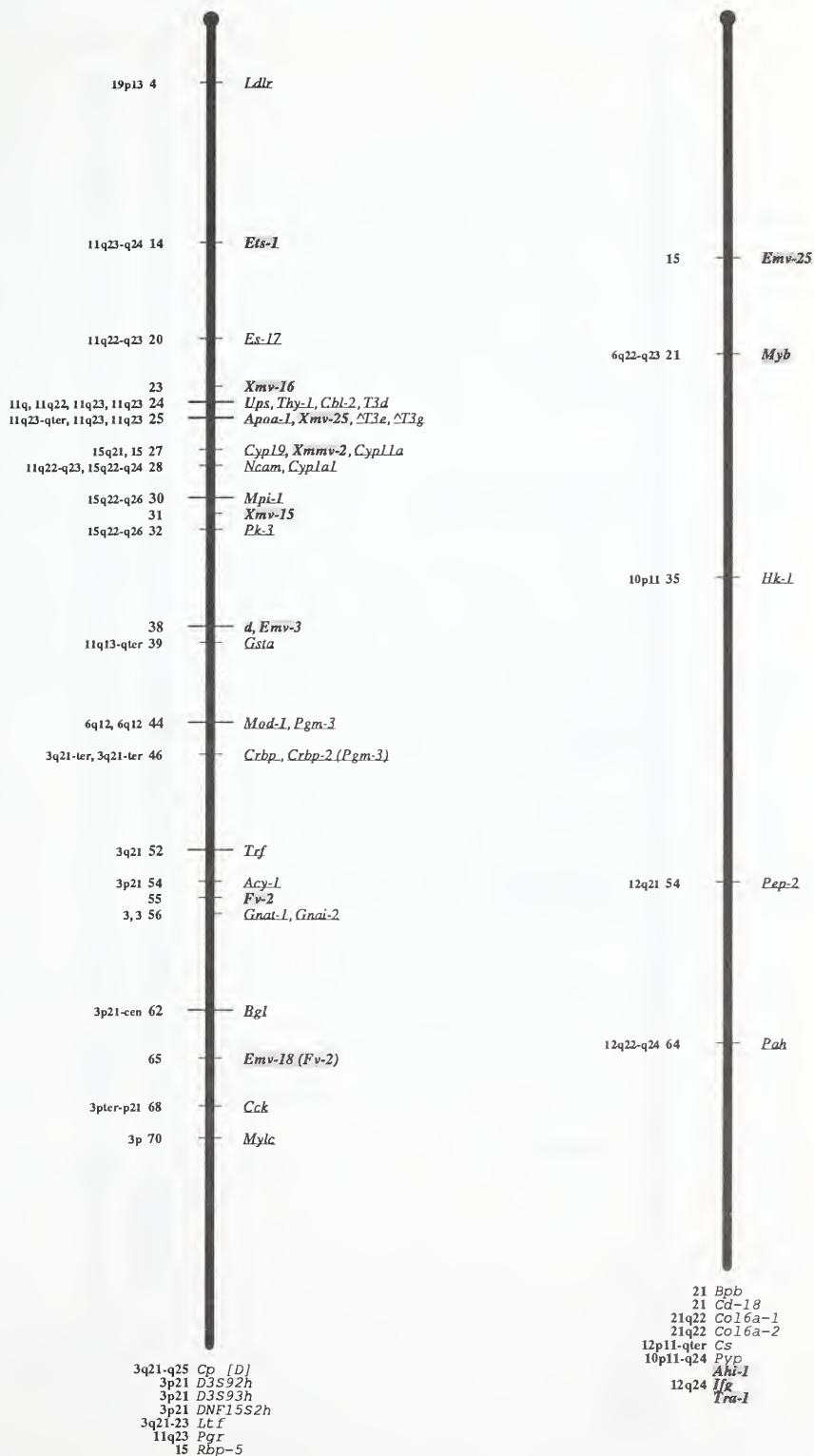


Chromosome 7



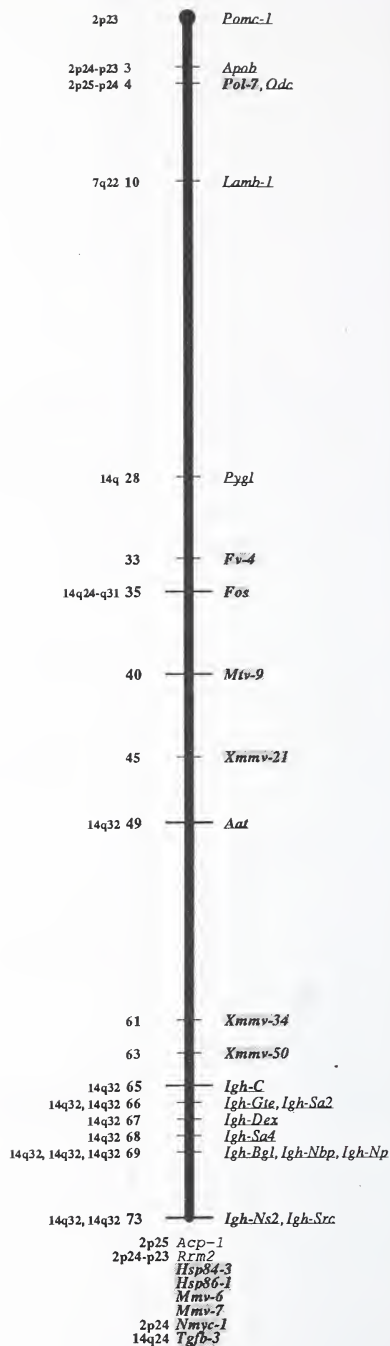
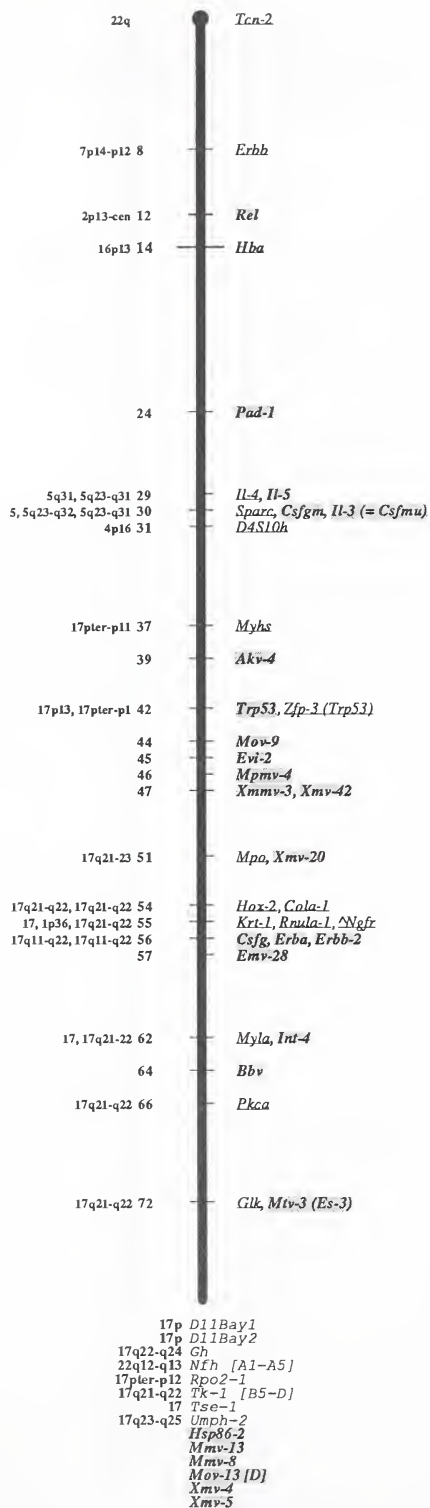
Chromosome 8



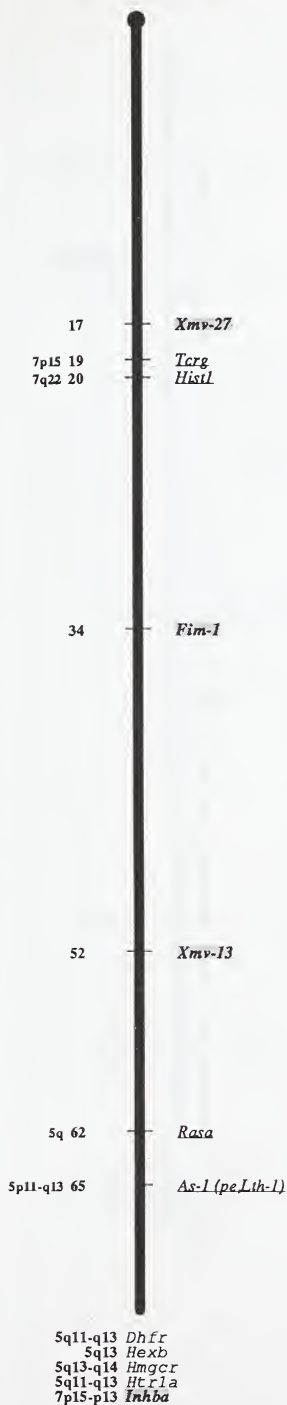


Chromosome 11

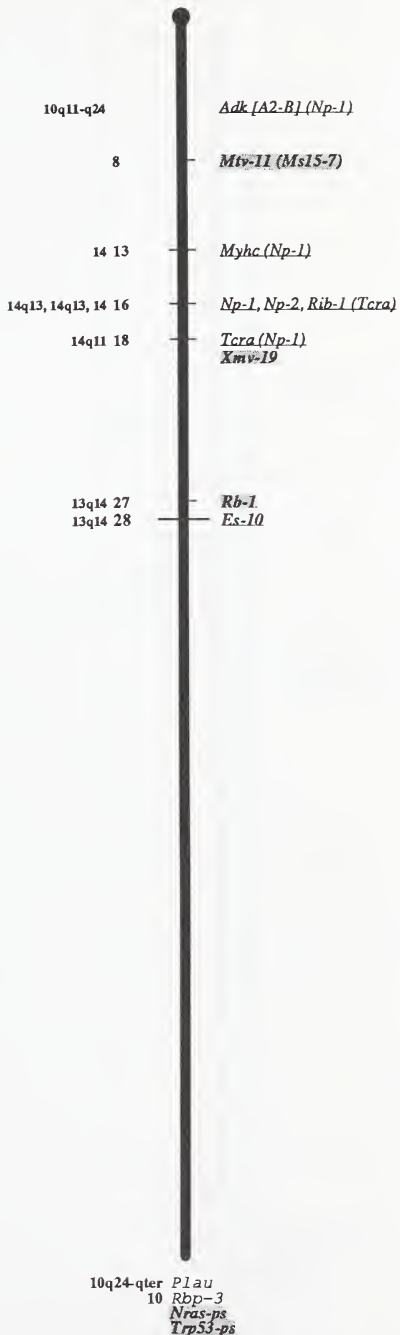
Chromosome 12



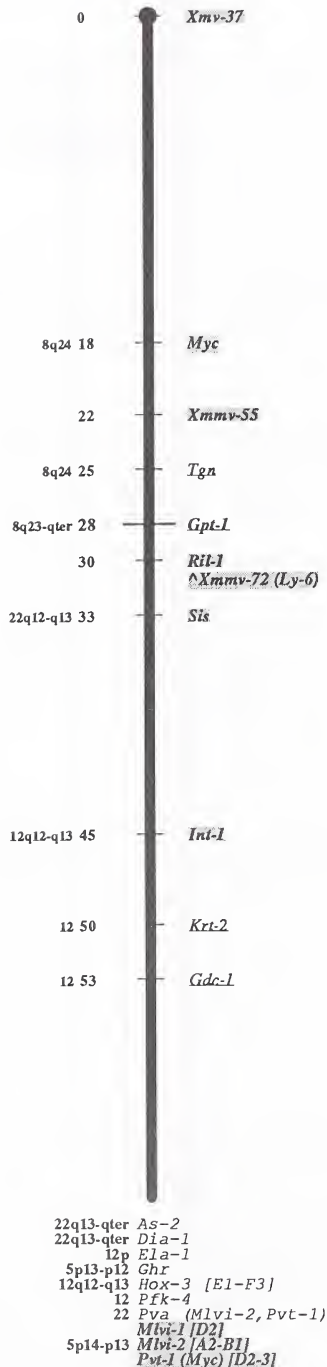
Chromosome 13



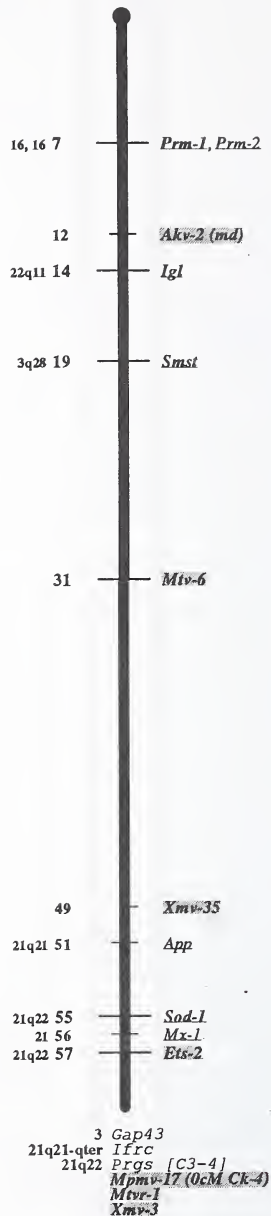
Chromosome 14



Chromosome 15



Chromosome 16



Chromosome 17

6q12-q21 *Sod-2 (Tcp-1)*
 6q25-q27 11 *Tcp-1*
 1 12 *Gnat-2 (Hba-4ps)*
 15 *Xmv-36*
 6p21, 6pter-q12 17 *Gla-1, Pim-1*
 21 18 *Cxv-1, Crya-1*
 6p21, 6p21 19 *H-2, Neu-1*
 19pter-p13, 6 21 *Pgk-2, Tpx-1*

26 *Hsp84-1 (H-2)*
 19p13 28 *C3*
 30 *Int-3*

21q22 *Cbs [cen-C]*
 6q26-q27 *Igf2r [A-C]*
 6p21 *Tnfa*
 6p21 *Tnfb*

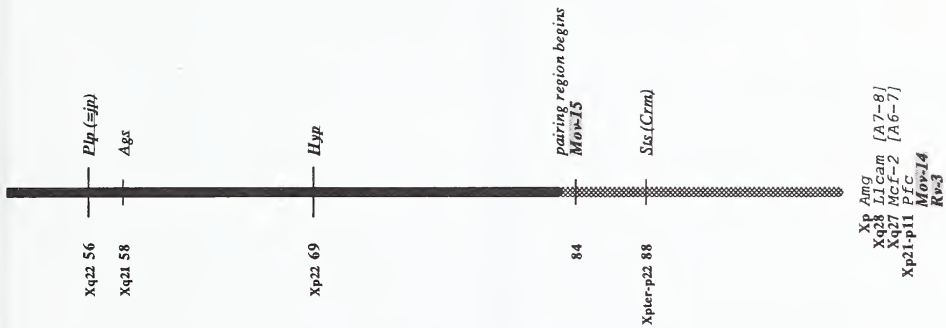
Chromosome 18

Mtv-2 (Tw)

30 *Emv-2I (pk)*

18q22-qter 57 *Mbp (≡shi)*

5q31-q32 *Badm*
 5q11-q13 *Gr1-1*
 5 *Ii*
 5q31-q32 *Pdgfr (Csfrmr)*
 18q23 *Pep-1*
 5q33 *Csfrmr [D]*
 Fim-2 [D]



Chromosome Y

Ycen-qter, Ypter-p11

Hya, Ndy

Mov-24

Xmv-Y

pairing region begins
Mov-15 (proximal to Sts)

Xmv-11
Xmv-40
Xmv-7

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CHAPTER 8

Legal and Ethical Issues in the Laboratory Assessment of Genetic Susceptibility to Cancer

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INTRODUCTION

The development of laboratory techniques for identifying carriers of cancer genes will be a major scientific breakthrough. Among other things, it may encourage lifestyle modification aimed at cancer prevention; eventually, it may even lead to therapeutic intervention. Genetic tests for cancer susceptibility also raise a number of difficult legal, ethical, and policy issues. Medical treatment, public health policy, insurance and employment screening, occupational and environmental regulation, commercial applications, and liability issues are some of the broad areas that will be affected.

This chapter will provide a brief overview of some of these potential issues. For the most part, however, there are no clear answers to the questions raised by genetic testing for susceptibility to cancer. Current laws in various areas were not designed for and are ill-equipped to regulate genetic testing. Moreover, a carefully considered national consensus on the ethical and health policy implications of genetic testing has not yet been developed.

CLINICAL APPLICATIONS

Americans are both health conscious and technology conscious. They learn of new medical developments through the news media or other sources and often believe that the latest in medical technology should be available immediately from their own physicians. "High tech" medicine is often equated with good medicine. Thus, the widespread introduction of much new medical technology, especially diagnostic technology, is patient driven.

It is foreseeable that the development of reliable and predictive laboratory tests to detect genetic susceptibility to cancer will spur a significant demand for their widespread clinical use. Eventually, genetic tests will not be limited to testing for rare disorders and cancers, but will be used to detect genetic predisposition to more common cancers.

The development of genetic tests of susceptibility to cancer will have major

commercial significance. It is easy to imagine numerous legal issues involving patent, antitrust, contract, and other areas of the law. There also could be pressure to regulate the licensing and use of the tests. For example, the Food and Drug Administration is currently considering whether to license one or more of various home test kits for HIV. The kits use blood or saliva, with the specimens either mailed to a laboratory or analyzed directly at home. Proponents argue that the kits will increase the accessibility of testing, thereby leading to earlier medical surveillance of seropositive individuals and to personal risk reduction to prevent the spread of the infection. Opponents contend that home testing will make population surveillance by public health officials more difficult. Most importantly, they argue there is an urgent need for face-to-face counseling when such disquieting information is obtained [1]. These same issues, especially with regard to the need for counseling, undoubtedly would be raised in considering whether to license home test kits for measuring genetic susceptibility to cancer.

Even the more traditional use of genetic tests, in the clinical setting, is not without its share of legal and policy concerns. Because there are fewer than 1,000 clinical geneticists in the United States, primary care physicians and not geneticists are likely to order most of these new genetic tests. This testing, however, must be performed with reasonable care, regardless of who is performing the testing.

The common-law rule applicable in every state is that a physician is required to use "that degree of care, skill and proficiency which is commonly exercised by the ordinary skillful, careful and prudent physician engaged in similar practice under the same or similar circumstances" [2]. The standard of care required of a specialist is higher. It is the degree of care, skill, and proficiency commonly exercised by a specialist in good standing [3].

The problem in satisfying these duties regarding genetic testing probably would not arise in offering testing or even in failing to offer testing [4]. It is more likely to arise from negligently interpreting test results or in failing to provide appropriate genetic counseling. For example, in several cases physicians and hospitals have been held liable for negligently performing amniocentesis tests and thereby failing to detect fetal genetic defects [5], failing to diagnose that a child's illness was caused by a genetic defect until after the parents had a second child with the same condition [6], or in negligently failing to diagnose a genetically defective fetus [7]. Plaintiffs allege that but for the act of negligence they would have aborted the genetically defective fetus or they would not have conceived another child.

New discoveries in genetics will place difficult demands on family practitioners, obstetricians, gynecologists, pediatricians, and other specialists. New genetic technologies, especially as related to the genetics of cancer, are complex. A familiarity with basic mendelian genetics will not equip a physi-

cian to understand hereditary polymorphisms of human drug metabolizing enzymes, cytogenetic measures of mutagenesis, and other new genetic tests to the degree necessary to provide effective counseling about cancer risk. Greater emphasis on genetics in medical school and in continuing medical education courses would appear to be essential.

A related issue is the duty to disclose genetic information to close relatives. Would a physician have a duty to disclose to a patient's close relatives (who may have a similar genotype) a test result of a genetic predisposition to cancer? Thus far, the law has been reluctant to impose liability on physicians for failing to notify third parties, except in extraordinary situations; for example, when a specific statute required physicians to notify the government in cases of suspected child abuse [8] and when a patient in psychotherapy disclosed a threat to kill a third party [9].

Despite the lack of case law, the President's Commission for the Study of Ethical Problems in Medical and Biomedical and Behavioral Research took the position that physicians *may* release genetic information to relatives without the patient's or client's consent if the following conditions are met: 1) reasonable efforts to elicit voluntary consent to disclosure have failed; 2) there is a high probability both that harm will occur if the information is withheld and that the disclosed information will actually be used to avert harm; 3) the harm that identifiable individuals will suffer would be serious; and 4) appropriate precautions are taken to ensure that only the genetic information needed for diagnosis and/or treatment of the disease in question is disclosed [10].

Courts are unlikely to impose a notification duty after genetic testing unless some medical intervention could prevent cancer from developing. For example, multiple polyposis of the colon, an autosomal dominant disease, leads to cancer of the colon around age 40, but it can be prevented by a prophylactic colectomy. A duty to disclose such a diagnosis to close relatives may be found to exist. There are limits, however, on disclosure. Imprudent, needless, or excessive disclosure could lead to liability for invasion of privacy.

PUBLIC HEALTH SCREENING

Public Health officials might be tempted to use genetic screening for public health purposes. There is certainly precedent for various types of institutional public health screening. Several forms of medical screening already take place in public schools, in the military, in prisons, prior to admission to hospitals, and in other public health settings. For example, state-mandated medical screening in public schools often includes hearing, vision, scoliosis, dental, and tuberculosis screening [11]. Although some institutional screening (eg, HIV testing and drug testing) is performed for the benefit of the institution or for persons other than the ones being screened, it is virtually certain that genetic

screening programs, if adopted, would be used to improve patient or family health.

It is important to consider the specific reasons why genetic screening for public health might be adopted. First, the tests could reveal important health information that would be otherwise unavailable to many people. An argument could be made that people who want to know their genetic profile have a right to obtain this information. Second, the tests could lead to cancer prevention through health promotion activities of those identified as genetically predisposed to cancer. Changes in diet, smoking, drinking, and environmental exposures may be prompted by identifying individuals at risk of cancer.

Both of these reasons, however, are debatable on policy grounds. First, unlike more traditional public health screening, the tests will probably be available before there is any direct medical intervention to prevent or cure the cancer. Second, the testing may require a substantial commitment of resources for laboratory work and pre- and post-test counseling that perhaps could be better utilized elsewhere. Third, there may be only a fine line separating voluntary health promotion from more coercive risk reduction measures. For example, there may be a temptation for prisons or the military to prohibit smoking by high-risk individuals or to place certain individuals on restricted diets. Fourth, the potential for stigmatization, discrimination, and psychological trauma may not justify genetic screening on a large scale.

REPRODUCTION

Because genetic traits are, by definition, heritable, it is likely that the entire field of human reproduction will be considered for possible application of genetic screening technologies. While reproductive planning, genetic counseling and other areas would appear to be greatly aided by new laboratory techniques to assess genetic susceptibility to cancer, a number of legitimate concerns also are raised by the prospect of widespread, or perhaps legally mandated, genetic testing.

Mandatory premarital genetic testing is one possibility. Virtually every state used to require (and many still require) a premarital test for syphilis [12]. The trend away from testing has been a response to the high cost-yield ratio of testing. Nevertheless, despite this record, and against the admonitions of public health officials, Illinois [13] and Louisiana [14] enacted laws mandating premarital HIV testing. It was not long, however, before these laws were repealed. The reasons for repeal were similar to those used in repealing syphilis testing: high cost-yield ratio, lack of a medical intervention for those testing positive, and couples circumventing the law by not getting married or getting married out of state [15]. Given this history, mandatory premarital

genetic testing would be difficult to justify. But, assuming such legislation were enacted, what would the state mandate as a result of the tests—gene therapy, genetic counseling, or some other measures?

The genetic screening of fetuses for cancer predisposition is much more likely. This voluntary testing could be easily incorporated into the battery of genetic tests already performed in amniocentesis and chorionic villus sampling. It is not clear, however, what the effect on abortion rates would be of learning that a fetus has a genetic predisposition to cancer. Following fetal genetic screening, abortion rates for muscular dystrophy, cystic fibrosis, and alpha- and beta-thalassemia are nearly 100%; they are 60% for hemophilia; and 50% for sickle cell anemia [16]. Abortion decisions based on genetic predisposition to cancer probably would depend on the type of cancer involved, the likelihood of cancer developing, the likely age of onset of the cancer, the possibility of treatment, and other factors. In any event, the development of new technologies with the potential to increase the rate of therapeutic abortions must be carefully considered in light of current legal uncertainties and moral divisions on the subject.

Another set of questions would arise if fetal gene therapy were available to treat the genetic defect. If the mother refused to consent to treatment, would the court appoint a guardian *ad litem* to order the treatment, much in the way that courts order blood transfusions for children? Could the failure to undergo fetal therapy lead to a prosecution of the mother for fetal abuse? Could an insurer or HMO threaten to withhold payment for childhood treatments unless the mother agreed to fetal gene therapy (or an abortion)?

Another possible time for genetic screening is during the neonatal period. For example, phenylketonuria (PKU) is relatively rare, with an incidence of one in 11,500. Yet, newborn screening for PKU (and congenital hypothyroidism) is required by statute in every state. Infants testing positive on a blood test can be placed on a low phenylalanine diet, thereby preventing mental retardation [17]. Tests for other congenital disorders, including homocystinuria, galactosemia, maple syrup urine disease, sickle cell anemia, cystic fibrosis, biotinidase deficiency, and congenital adrenal hyperplasia, are performed in some states [18]. Mandatory neonatal genetic screening for cancer susceptibility appears to be appropriate only if an effective medical intervention is possible during the neonatal period.

The enactment of legislation requiring genetic screening of the type mentioned above may be preceded by a common law duty for individuals to undergo testing or to inform other parties about test results. For example, individuals attempting to parent children or engaging in sexual activity when conception and childbirth are foreseeable consequences may have a duty to inform their partners about their genetic profiles. The failure to do so could lead to liability for battery, fraud, negligence, intentional infliction of emo-

tional distress, or other torts. Actions brought against one parent by the other parent or by the child are possible. This would represent an attempted expansion of the currently recognized duty of individuals to inform their sexual partners if they have any sexually transmissible diseases [19].

Genetic testing and disclosure responsibilities also may arise from new, noncoital reproductive technologies. There may be a duty to screen sperm and ova used in in vitro fertilization, to screen sperm donations used by sperm banks, and to screen surrogate mothers. Laws already have been enacted in several states requiring genetic testing [20]. The failure to test or to inform other parties about test results also could lead to civil liability if the child later developed a genetically related illness, including cancer.

There are a variety of ways in which the issue of genetic testing could arise. For example, in one case, a mother placed her newborn son up for adoption with a private adoption agency in 1967. The adoption agency learned by 1971 that the child suffered from combined severe immune deficiency (CSID or SCID), an X-linked inherited disease manifested in male offspring, but it failed to inform the biological mother that she was a carrier and future sons might be similarly affected. The mother married in 1975 and had a daughter in 1980 and a son in 1983. The son born in 1983 died at the age of six months. After discovering that her first son had CSID, the mother sued the adoption agency for failing to inform her that her first son had a genetic disease. The California Court of Appeals held that the adoption agency had no duty to warn the mother; therefore, it could not be found liable [21].

A somewhat different result was reached in a Wisconsin case [22]. In 1979 a couple that was considering adopting a 23-month-old child was told by the adoption agency that the child's paternal grandmother had died of Huntington disease. The couple was also incorrectly told that the child's father had "tested negative" and therefore the child had no chance of developing the disease. In 1984, after the development of a gene probe for Huntington disease, the child was diagnosed as a carrier. The adoptive parents then filed a lawsuit in which among other things they sought damages for the substantial medical expenses the child would be certain to incur. The Supreme Court of Wisconsin held that even though the adoption agency had no duty to discover and disclose health information about the children they place for adoption, the agency had assumed the duty by affirmatively misrepresenting the child's chances of developing Huntington disease.

These two cases illustrate the unsettled state of the law with regard to the duty to disclose information about genetic diseases in one narrow setting. Undoubtedly, other legal actions could be brought if the illness were a genetically related childhood (or even adult-onset) cancer. Eventually, it even could be asserted that fragile site, acetylation polymorphism, or other labora-

tory techniques should have been used to discover a genetic predisposition to cancer.

Finally, it must be remembered that the use of genetic information in the area of reproduction is certain to raise strong emotional issues and the specter of eugenics. For lawyers, this is epitomized by the 1927 Supreme Court decision in *Buck v. Bell* [23]. At issue was the constitutionality of a Virginia law authorizing the superintendents of state mental institutions to sterilize "any patient afflicted with hereditary forms of insanity, imbecility, etc." Carrie Buck was an 18-year-old, "feeble-minded" woman residing in a state institution. Her mother was also "feeble-minded" and resided in the same institution and Carrie Buck had previously given birth to an illegitimate, "feeble-minded" child.

In upholding the constitutionality of the statute, Justice Oliver Wendell Holmes stated:

"It is better for all the world, if instead of waiting to execute degenerate offspring for crime, or to let them starve for their imbecility, society can prevent those who are manifestly unfit from continuing their kind. . . . Three generations of imbeciles are enough" [24].

Although *Buck v. Bell* has never been overruled, it certainly would not be followed today. Nevertheless, it is a stark reminder of the dangers of letting ethics and jurisprudence be dictated by the "scientific truths" of the day.

INSURANCE

If new technologies were developed to determine genetic susceptibility to cancer, both health and life insurance companies would be extremely interested in the tests. Health insurance is either individual or group. An individual health insurance contract runs between the insurance company and the insured individual. On the other hand, a group health insurance contract runs between the insurance company and a sponsor (usually an employer) that is the insured party. These contracts are continuous and survive the membership of any particular members of the group.

Group health insurance is generally issued without a medical examination or other evidence of insurability. (This is a particularly attractive feature for many individuals.) Insurers have found that medical examinations are not cost effective; they are only interested in whether the group as a whole is insurable. In a large group of employed persons (and their dependents), it is presumed that the overall risk for the group is close to average.

By contrast, applicants for individual insurance are not part of a well-defined, homogeneous, and generally healthy group. Because of the potentially great differences in health status and potential risks presented to insurers by

individual applicants, insurers evaluate individuals by applying medical underwriting criteria.

Life insurance underwriting more closely resembles individual health insurance underwriting. A health history questionnaire, attending physician statement, physical examination, and blood and urine screening may be required—depending on policy amount, applicant age and health history, or other factors. From an insurer's perspective, medical underwriting is defensive; it is designed to protect the company against "adverse selection." In essence, the principle of adverse selection postulates that individuals who know that they are at the greatest risk are more likely to seek insurance coverage and in higher amounts. Without equal access to medical information (ie, prior test results of applicants or insurer-ordered tests), insurers could not engage in the necessary risk underwriting. Consequently, insurance companies either would lose substantial amounts of money on claims or they would raise the premiums of all policyholders so that low-risk policyholders subsidize the rates of those at high risk.

The controversy surrounding HIV testing by life insurance companies offers an insight into the kinds of concerns that likely would be raised about genetic testing by life insurers [25]. From an actuarial standpoint, HIV testing is abundantly reasonable; from a social and political standpoint it is more controversial—especially because the exclusions from coverage fall disproportionately on certain groups. Thus, genetic testing by life insurers is more likely to be contentious if the exclusions similarly had such group-based effects. Because genetic diseases often tend to be related to ethnicity, exclusions from insurance could also raise claims of discrimination. Moreover, in the age of computers, there is a well-founded concern that sensitive medical information in the possession of a single source could be disseminated on a wider basis without the knowledge or consent of the individual.

The legal and policy issues in health insurance underwriting are quite different from the issues involved with life insurance underwriting. Life insurance is not a necessity, but health insurance is. In our society, access to quality health care depends on access to health insurance. In 1988 there were about 37 million Americans without health insurance, up from 30 million in 1980 [26]. Genetic screening for susceptibility to cancer could have the effect of increasing the number of uninsured or, through exclusion waivers, eliminating cancer coverage for a large group of individuals. By excluding from private insurance coverage those individuals who are most likely to need it, substantial new health care demands would be placed on government, charities, and providers of uncompensated care. Even without major changes in our health care system, such as a national health insurance system, there may be significant public pressure to prohibit genetic testing by health insurers.

EMPLOYMENT

During the early 1980s public attention was called to the practices of a few employers that performed biochemical genetic tests on employees. Screening for sickle cell trait, thalassemia, glucose-6-phosphate dehydrogenase deficiency, serum alpha₁-antitrypsin deficiency, and other biologic markers had been suggested in some of the scientific literature as a way of screening "hypersusceptible" individuals out of work environments that were likely to cause occupational illness [27]. By virtually all accounts, this type of genetic screening is performed rarely, if at all, today because of the adverse publicity following congressional hearings in 1981 and 1982 and the publication of a report in 1983 by the Congressional Office of Technology Assessment which was critical of the practice [28].

If there is a resurgence of genetic screening in the workplace, it is unlikely to be similar to the prior episode of genetic screening for occupation-related susceptibilities. The newer form of genetic screening is almost certain to be screening for nonoccupation-related illnesses and the driving force will be the escalating costs of employee health benefits.

In 1988 employers spent \$2,354 per employee on health benefits and, despite aggressive cost containment measures, costs increased an average of 18.6% over 1987 levels [29]. According to "conventional wisdom," if potential "high cost" employees could be kept out of the work force, then health care costs could be controlled. These medical screening strategies already have been implemented by employers. HIV testing, refusals to employ cigarette smokers, and other forms of workplace medical screening already in use make it clear that employers would be interested in genetic screening. Moreover, legislation mandating employers to provide all employees with health insurance (adopted in Hawaii and Massachusetts and under consideration in Congress) might have the effect of encouraging even more widespread medical screening, including genetic screening.

It is far from settled whether genetic screening by employers would be legal. If the screening practice had a disparate impact along the lines of race, color, religion, sex, or national origin, then the screening might violate Title VII of the Civil Rights Act of 1964 [30], the primary federal law prohibiting certain forms of discrimination in employment. More likely, genetic screening could be challenged as violating the federal Rehabilitation Act [31] or state laws [32] prohibiting discrimination in employment against otherwise qualified handicapped individuals. There are many unresolved issues, however, under handicap discrimination law, such as whether a refusal to employ a healthy, asymptomatic individual because of a risk of cancer in the future constitutes discrimination on the basis of "handicap." Another issue is whether concern about future health care costs is a valid defense.

During the 1970s, Florida [33] and Louisiana [34] enacted specific genetic testing laws that prohibit discrimination in employment based on sickle cell trait; North Carolina prohibits employment discrimination based on sickle cell or hemoglobin C trait [35]; and a 1981 New Jersey law prohibits discrimination based on sickle cell trait, hemoglobin C trait, thalassemia trait, Tay Sachs trait, or cystic fibrosis trait [36]. Other, more inclusive, state laws could be passed if genetic testing reemerges. At the very least, existing handicap discrimination laws need to be clarified through amendment or case law.

The relationship between national employment policy and national health policy also must be considered. Approximately two-thirds of all Americans obtain their health insurance through employer-provided group health insurance [37]. Individuals who are excluded from the primary work force because of their high risk of future health problems are unlikely to be able to obtain or afford more expensive individual health insurance coverage for themselves and their dependents. Therefore, detailed genetic screening of workers for susceptibility to cancer could lead to an increase in the number of people without health insurance. This, in turn, would have pronounced social consequences. The issues of employment, insurance, and health policy are very much interrelated [38].

Another possible employment-related use of genetic tests of cancer susceptibility is in regulating workplace exposures to carcinogens. Certain genetic traits have been associated with particular occupationally induced cancers, including aryl hydrocarbon hydroxylase inducibility and susceptibility to lung cancer and acetylation phenotype and susceptibility to arylamine-induced bladder cancer.

Under the Occupational Safety and Health Act, genetic tests could be required before a worker is assigned to an area where there is exposure to certain carcinogens. Periodic cytogenetic monitoring also could be required to measure the levels of sister chromatid exchanges and other chromosomal aberrations in attempting to study the cellular effects of exposure to clastogens. These data could be used to set safe exposure levels and in the medical-removal of workers who were beginning to display the cytogenetic evidence of exposure. A similar use of genetic monitoring and genetic epidemiology in standard setting could be used under the environmental protection laws.

CONCLUSION

The ability to assess genetic susceptibility to cancer is certain to raise a wealth of legal and ethical issues. Some brief mention has been made of the issues surrounding clinical applications, public health screening, reproduction, insurance, and employment. The fact that such difficult issues are likely to emerge does not suggest that science should not proceed. It does suggest,

however, that thoughtful and comprehensive social policies and necessary legislation should be developed simultaneously with the scientific advances.

RECOMMENDATIONS

1. Consideration must be given to the funding of research on genetic testing, to the certification of test procedures, to the regulation of laboratories and test kit makers, and to the expansion of professional and lay educational programs in genetics.

2. Consideration must be given to whether or when it is appropriate to require, permit, or prohibit the use of tests for the assessment of genetic susceptibility to cancer, including testing in the clinical and public health settings.

3. Consideration must be given to the permissible uses of information yielded by tests of genetic susceptibility to cancer, particularly by employers and insurers, and to the safeguards necessary to ensure the privacy of this information.

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Genetic Services *for* Underserved Populations



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In Maternal and Child Health





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FOREWORD

This is the third publication presenting issues in genetics that results from the active collaboration between the March of Dimes Birth Defects Foundation and the federal Maternal and Child Health (MCH) program. During the decade of the 1980s, our two programs supported three symposia that explored critical topics in genetic services. Each symposium was followed by a publication of its proceedings with wide dissemination to the field.

In the spring of 1983, a national symposium on "Genetic Disorders and Birth Defects in Families and Society: Toward Interdisciplinary Understanding" was held in Baltimore. It was a landmark in the process of understanding the impact of genetic disorders on affected families and society in a time of ever increasing scientific advancements. It was the first national, broad, interdisciplinary conference dealing with educational needs and advocacy issues.

Two years later, in 1985, the second symposium, "Genetic Support Groups: Volunteers and Professionals as Partners," took place in Washington. It reflected the growing movement toward self-help in dealing with these problems. A national alliance of group representatives emerged at the symposium, which became the foundation for the Alliance of Genetic Support Groups.

The third symposium of the decade, "Genetic Services for Underserved Populations," was held in Washington in May 1989. It was directed at special populations receiving inadequate health services, including genetic services. Participants recognized that rapid-growth racial and ethnic minority populations; the switch in sources of migration from western and southern Europe to Asia, Central America and eastern Europe; religious differences; and economic disadvantages are among the contributing factors to this underservice. This proceedings contains discussion of these and other issues and strategies and recommendations to overcome them.

We thank the many individuals and organizations that made these symposia possible and productive. The public-private partnership between the March of Dimes and MCH, in collaboration with our friends, over the past decade has been an important force in the development of genetic services in the nation.

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INTRODUCTION

ROCHELLE MAYER, Ed.D. SYMPOSIUM DIRECTOR

These are the proceedings of the National Symposium on Genetic Services for Underserved Populations that took place in May 1989. The purpose of the symposium was to promote maximum health care in human genetics for the underserved populations in the U.S. The symposium brought together nearly 200 professionals, consumers, and representatives from organizations and programs to assess the scope of the problem, identify barriers to care, discuss strategies and model programs and generate recommendations for overcoming barriers. These proceedings should be of value to health care consumers and professionals who are concerned with the provision of genetic services to underserved populations.

A large proportion of the United States population receives inadequate health care because of one or more of the following factors: ethnocultural distinctiveness, geographic isolation, language barriers, religious beliefs, personnel shortages, racial differences, and economic disadvantages. Medical genetics services are inaccessible for the same reasons, and for several others. First, genetics services are largely preventive, and in most attempts to rectify maldistribution of health care, preventive services are often neglected. Second, medical genetics has traditionally been considered a subspecialty of limited applicability to only a few people. In reality, medical genetics is increasingly relevant to most diseases, including the most common ones. The development of new technology, such as DNA diagnosis, is rapidly bringing genetics services into the medical and public health mainstream. If the entire population is to derive optimal benefit from the current application and future promise of medical genetics, then the factors that define the genetically underserved must be enumerated and analyzed.

Since the mid-1970s, there have been federal initiatives to address the need for genetic services to underserved populations, beginning with the National Sickle Cell Anemia Control Act of 1972. Funding in the form of special projects of regional and national significance (SPRANS, Office of Maternal and Child Health) and services provided at the state level within the Maternal and Child

Health Block Grant, as well as efforts spearheaded by voluntary organizations such as the March of Dimes Birth Defects Foundation (MOD) and the National Organization of Rare Disorders (NORD), have also addressed this need. However, many issues related to the provision of genetic services to underserved groups remain unresolved, and services remain inadequate. Issues that need to be addressed include understanding the barriers to the user (financial, language, cultural) and to the providers (lack of knowledge of genetic disorders in minorities, unfamiliarity and lack of sensitivity to cultural differences and language) which keep the underserved from accessing services.

The National Symposium on Genetic Services for Underserved Populations is the third in a series of national symposia focusing on core issues in the delivery of genetic services. We have been fortunate to have leadership from the Mid-Atlantic Regional Human Genetics Network (MARHGN) that has, over the years, fostered the development of these national forums; and we have been fortunate to receive the continuing support of the March of Dimes Birth Defects Foundation (MOD) and the Genetic Services Branch, Office of Maternal and Child Health (OMCH), to co-sponsor these symposia.

The first national symposium, "Genetic Disorders and Birth Defects in Families and Society: Toward Interdisciplinary Understanding" took place in 1983 in Baltimore, Maryland, to consider the social and psychologic impact of genetic disorders on families and society. One clear message from the first symposium was the need for voluntary genetics organizations to share information with one another and with professionals. The second national symposium, "Genetic Support Groups: Volunteers and Professionals as Partners" held in 1985 in Washington, D.C., responded to this need by bringing together genetics service providers, organizers of voluntary groups, and parents. An outgrowth of that symposium was the development of the Alliance of Genetics Support Groups, a network of voluntary genetics organizations founded to help groups establish a link with research communities, promote public education, and provide a mechanism for sharing information. The goal of the third national symposium was to promote maximum health care in human genetics for underserved populations in the United States.

The objectives of those who planned the symposium, and of the writers of the chapters of this book, include the following:

1. Identify existing services.

2. Promote access to and utilization of existing services.
3. Identify gaps in services to underserved populations.
4. Provide recommendations for the development of new services where necessary to reach the underserved.
5. Provide recommendations for the promotion of the establishment of a constellation of comprehensive services including follow-up.
6. Provide recommendations for delivering services in a culturally relevant and sensitive manner.

The book is divided into the three major themes of our symposium: Scope of the Problem; Barriers to Care; and Strategies and Model Programs. A fourth section presents the strategies and recommendations generated at the symposium. Part I provides the consensus recommendations. These were developed by the executive planning committee and plenary session chairs who reviewed and distilled the recommendations from thirty workshop sessions into eight thematic areas of concern: ethnocultural considerations, economic and insurance considerations, coordination of services, education, life cycle considerations, consumer empowerment, geographic considerations, and legislation. Part II consists of the complete recommendations which were generated in the individual workshops.

The first draft of the consensus and workshop recommendations were presented at the close of the symposium and participants were invited to comment on all portions of the recommendations. This version of the recommendations integrates those suggested changes. Recommendations generated at the National Symposium on Genetic Services for Underserved Populations have been submitted to the executive committees of the Council of Regional Networks for Genetic Services (CORN) and the Alliance of Genetic Support Groups to develop strategies for implementation.

It was a great honor to be Symposium Director of the National Symposium on Genetic Services for Underserved Populations. I am indebted to the members of the planning committee and the theme chairs for contributing their time, talent and energy to ensure that the symposium fulfilled its mission. I am also deeply grateful to the staff of the National Center for Education in Maternal and Child Health for their help in performing so many tasks related to the

symposium and the production of these proceedings with competence and dedication. I especially want to thank Dr. Robert C. Baumiller, S.J., Director of the National Center for Education in Maternal and Child Health, for his encouragement and dedication of resources to this symposium.

Theme **I** *the* Scope
of the Problem



PLENARY SESSION

KEYNOTE ADDRESS

JAMES E. BOWMAN, M.D.

BACKGROUND

The development of techniques for the diagnosis of genetic disorders before and after birth stimulated a revolution in medical genetics. Prior to these discoveries, genetic counseling for the prevention of genetic disorders for couples at risk concentrated exclusively on abstinence, contraception, sterilization, artificial insemination, adultery, and divorce. The development of a variety of tests for high frequency genetic disorders in the newborn and the general population was followed by education, testing, and counseling of high-risk populations by private organizations, mandatory and voluntary state programs, and voluntary federal programs under the auspices of the National Sickle Cell Anemia Control Act, Tay-Sachs disease legislation, the Genetic Disease Act, and other legislation. Ostensibly, the triad of education, testing, and counseling identified individuals and couples at risk, so that they could make informed decisions about reproduction and health.

These were noble objectives, but it is unlikely that Congress would have appropriated millions of dollars over the past 17 years for genetic education, screening, and counseling programs unless the lawmakers believed (or were led to believe) that there would be a significant reduction in the incidence of genetic disorders. Eradication, elimination, and control were inveterate code words in testimony before Congress in support of genetics legislation, and members of Congress clutched these harmful words. Recall the title of the sickle hemoglobin legislation: "Sickle Cell Anemia Control Act." The title is unfortunate because the only means to "control" sickle cell anemia are unsavory, even today.

Roe v. Wade, which legalized abortion, broadened medical indications for ultrasound visualization of the fetus, and escalated techniques for amniocentesis, chorionic villous biopsy, and a spectrum of tests for prenatal diagnosis. Wrongful birth and wrongful life court decisions followed—which would have been illegal without Roe—and ensured that women would be counseled

about prenatal diagnosis and the option of abortion of fetuses with genetic and other disorders. Women who were at risk—and who previously avoided pregnancy for fear of having children with severe birth defects—now elected pregnancy.

Holtzman [1] pointed out that commercial interests will focus on population screening, rather than on testing in families in whom disease has already occurred. He indicated that the number of individuals screened for only a few common disorders could well exceed 10 million per year, entailing 18 million tests, of which more than 1.2 million would be positive. Further, screening of young women to determine their carrier status or of all pregnant women for chromosome disorders would involve more than 4 million tests, out of which about 46,000 would be positive. Such numbers far exceed the capacity of genetic service centers.

But let us examine the plight of the subjects of this conference: the underserved.

THE POOR

Smeeding and Torrey [2] described the problems of poor children in rich countries, which included Australia, Canada, Sweden, United States, United Kingdom, and West Germany. The United States had the highest poverty rate among children and the second highest poverty rate among families with children. Not surprisingly, the poverty rate among black children was three times as high as among white children, and the poverty rate of Hispanics was double that of white children. Even so, the poverty rate among white children was 11.4%, a rate that was higher than that of all children in the other countries, except Australia. In Canada, the poverty rate of minority and non-minority populations (both 9.6%) was lower than that of U.S. white children alone.

I quote from Reich [3]:

Since October 1981, the poor and near-poor in America have lost more than \$10 billion in federal support. Some 661,000 children have lost Medicaid coverage; 900,000 poor youngsters no longer receive free or reduced-price lunches; 280,000 no longer receive free or reduced-price breakfasts; 150,000 poor working families have lost eligibility for government-supported day care; 200,000 fewer pregnant women, new mothers, infants, and children are

getting special federal coupons for milk, juice and other diet supplements. One million people have been dropped from the food stamp rolls. In addition, 890 school districts have cut back on special education programs.

Almost daily, physicians repeat the shibboleth that health care resources are scarce. Yes, health care resources are scarce, but *only for the poor*. Physicians have abrogated their responsibility to patients, and allowed administrators and economists to impersonalize health care policy to such an extent that millions of Americans have limited to no access to health care, even in university medical centers. The federal government, the states, organized (disorganized) medicine, and university hospitals all blame each other for our abysmal health care system. Unfortunately, American human rights activists travel far and wide ferreting out human rights violations abroad, and ignore our own human rights infamy: neglect of the plight of poor children and adults in the United States.

INFANT MORTALITY

The infant mortality rates in the United States for blacks far exceed those for whites [4]. During the period 1979–1981, the number of infant deaths per 1,000 live births was 11.0 for whites and 21.0 for blacks. The region with the highest infant mortality was the east north central region, which includes Ohio, Indiana, Illinois, Michigan, and Wisconsin. The overall rate for this region was 23.8. The areas with the highest infant mortality rate for blacks were Delaware, 27.4; the District of Columbia, 26.3; Illinois, 25.9; and Utah and West Virginia, 23.2. The United States ranked 15th in the world for infant deaths. The infant mortality rate of the 25th country, Cuba, was 18.5, lower than that of blacks in the United States [5]. Consequently, although we are the most developed of all countries, we have shameful pockets of underdevelopment within our own borders. Ironically, if *Roe* is repealed, some of the states with the highest infant mortality rates—such as Illinois—would be among the first to ban abortion.

MATERNAL MORTALITY

The age-adjusted maternal mortality rate for complications of pregnancy, childbirth, and the puerperium in 1981 for white females was 6.5 (per 100,000 live births) and 22.1 for black females [4]. Nevertheless, the Governor of California recently ordered the county hospitals not to accept pregnant women

for prenatal care, but they could enter county hospitals for delivery (D. Cunningham, personal communication, 1988). Interestingly, California has one of the best prenatal and population-screening programs for a variety of genetic disorders.

If a major thrust of genetic educational programs is directed to couples before marriage, what about children who are born out of wedlock? Unfortunately, this vital issue is studiously overlooked in most genetics programs [6,7].

OUT-OF-WEDLOCK BIRTHS

Wilson [8] asserted that the black out-of-wedlock birth ratio increased precipitously, not because the rate of extramarital births increased, but because the percentage of women married and the rate of marital fertility both declined. To compound the problem, Wilson showed that the proportion of never married black women increased from 65% in 1965 to 82% in 1980 for ages 14 to 24 and from 8% to 21% for ages 25 to 44. Wilson reported that the poverty rate of female-headed families was 36.3% in 1982, but the rate for married-couple families was 7.6%. Finally, Wilson indicated that the increasingly critical jobless rate for black males contributed to the out-of-wedlock birth rate, because women see little advantage in marrying a jobless man.

Extramarital sex is not confined to the black community; it is increasing, particularly among teenagers. A national research panel [9] recently reported on social behaviors that spread Acquired Immune Deficiency Syndrome (AIDS). Some studies demonstrated that three-fourths of all girls had sex during their teenage years and that 15% had four or more partners. According to Williams [10], of the one million teenage Americans who become pregnant each year, about 400,000 obtain abortions, 470,000 complete the pregnancy, and the others miscarry.

A recent issue of *Health United States* (1986) showed that births among unmarried women more than doubled from 1970 to 1986, from 11% to 23% of all births. In 1986, 11% of women of Asian and Pacific Islander descent who gave birth were unmarried, compared with 16% of white women, 42% of Native American women, and 61% of black women [11]. A large proportion of the increase was because of teenage pregnancy. I introduce these social problems because if genetics education, testing, and counseling programs are to have any

affiliation with reality, the quandary of children who bear children must be recognized as a major health problem.

THREE PLAGUES: POVERTY, DRUG ADDICTION, AND AIDS

A *New York Times* editorial in 1989 [11] outlined three plagues that blight the South Bronx in New York City: poverty, drug addiction, and AIDS. Among emergency room patients tested at Bronx Lebanon Medical Center, 23% were infected with the AIDS virus. In one South Bronx district, one in twenty-five pregnant women carried the virus, and about one-third to one-half of their babies will be infected with an incurable disease that will cost upward of \$100,000 per affected child, with death the end result. The people of the South Bronx are mainly black, or Hispanic, and poor.

Any genetics program in the black and Hispanic community that does not take these social, economic, and health factors into consideration will have almost no prospect for success. Unfortunately, it is unlikely that we will legislate mandatory equitable education, decent housing, health care for all, and full employment, to alleviate the predicament of the poor. If we ask poor women to cooperate in community genetics programs, and disallow universal prenatal care, equitable health care delivery, and disregard the appalling social and economic conditions in this country, we are then conspirators in health care deceit.

Let us not forget the rural areas in the United States, where health care is commonly inadequate. Even so, it would be callous indeed to introduce genetics programs in isolated regions unless they are integrated into a health care delivery system. There are excellent outreach genetics programs in south Alabama, Utah, and in the greater Baltimore region associated with medical centers, but representatives from these regions should discuss these programs.

ABORTION INEQUALITY

Even though the Supreme Court decision in *Roe v. Wade* legalized abortion under certain conditions, indigent women discovered that although Medicaid paid for the care of pregnancy, many states would not pay for an abortion unless there was a medical necessity. An indigent woman filed suit in an attempt to have the state pay for an abortion. The Supreme Court in *Maher v. Roe* [12] ruled against the woman despite the poignant dissent of Mr. Justice Brennan, Mr. Justice Marshall, and Mr. Justice Blackmun, from which I quote, in part:

But a distressing insensitivity to the plight of impoverished pregnant women is inherent in the Court's analysis. The stark reality for too many, not just "some," indigent women is that indigency makes access to competent licensed physicians not merely "difficult" but "impossible." As a practical matter, many indigent women will feel that they have no choice but to carry their pregnancies to term because the state will pay for the associated medical services, even though they would have to have abortions if the state had also provided funds for that procedure. This disparity in funding by the state clearly operates to coerce indigent women to bear children they would not otherwise choose to have, and just as clearly this coercion can only operate upon the poor, who are uniquely the victim of this form of financial pressure.

Mr. Justice Frankfurter's words are apt:

To sanction such a ruthless consequence, inevitably resulting from a money hurdle erected by the state, would justify a latter day Anatole France to add one more item to his ironic comments on the "majestic equality" of the law. The law, in its majestic equality, forbids the rich as well as the poor to sleep under bridges, to beg in the streets, and to steal bread. . . .

A 1988 editorial in the *New York Times* [13] stated that the U.S. Department of Health and Human Services issued regulations banning federal funds to clinics that offer abortion counseling. It was pointed out that should these rules take effect, four million—mainly poor women—who depend on federally supported family planning clinics, would suffer. These women would be denied access not only to abortion, but also to medical information that would keep them from becoming pregnant. The editorial asked how a physician, forbidden under the regulations to even mention the word abortion, could help a woman make an informed choice about family planning. Further, "and how cruel that a poor woman can't be told that an abortion is a legal option—and given a referral if she requests one—compared with the woman who can afford a private doctor." It was also asserted that in the United States, there are two kinds of family planning counseling: one for the affluent (and the middle class), and

one for the poor. The options given the poor in genetic counseling are similarly segregated in the 37 states that do not allow public funding for abortion.

Legislation, court decisions, state and federal genetics programs, and scholars in the social sciences, the humanities, law, medicine, and genetics, however, all support discoveries in genetics that now facilitate genetic testing, prenatal diagnosis, and selective abortion of fetuses with genetic and other disorders. Under tort, battery, and common law, physicians and other health workers have been found liable for malpractice if they do not inform prospective parents of the risk of the birth of children with genetic disorders, and the option of prevention by prenatal diagnosis and abortion.

Public funds are spent on research in genetics and for genetic education; screening; and counseling programs for intractable disorders which can often be prevented only by prenatal diagnosis and selective abortion. Public monies are also spent on research to improve techniques of prenatal diagnosis, with a potential end result of selective abortion. Poor patients are encouraged by state and federal genetics programs to participate; they are led to the brink, and then must be told that support ends here. Ironically, the poor are neglected, but scientists are not. If *Roe* is overturned, or if abortion is limited to cases of rape, incest, or to save the life of the mother, the middle and upper class will either experience what the poor have had to endure—or fly to Sweden, as they did before *Roe*.

A pro-choice statement issued by the Genetics Task Force of Illinois in May of 1989 is significant, for it represents the first time that a genetics organization has had the moral courage to make a public statement on behalf of their patients to have access to pregnancy termination, if they so wish. This important document will now be quoted in full:

The Genetics Task Force of Illinois, Inc., is an organization composed of genetic counselors, physicians, genetic laboratory directors, and other professionals involved in the delivery of clinical genetics and prenatal diagnostic services, and/or research in medical genetics within the state of Illinois.

Our patient population consists of individuals who have a genetic disorder, parents who have a child with a genetic condition or birth defect, high-risk pregnant women, and persons with a family history of a genetic disease or birth defect. All of these individu-

als may have a significantly increased risk for an abnormal pregnancy outcome.

As members of this organization, we support any pregnant woman's option of a confidential, safe and legal termination as a component of comprehensive genetic services. Denial of this medical procedure could have adverse physical, mental, and financial consequences to our patients.

(This statement was added after the conference, because it had not then been released for the signature of the members who were also willing to go on public record.)

Although poor persons may be denied public funds for abortion, the Supreme Court authorized sterilization of poor women to limit the number of children who were supported by public funds. The Court, in the case of *Dandridge v. Williams* [14], upheld the legality of a maximum welfare grant imposed by the state of Maryland. This regulation restricted total state Aid for Dependent Children (AFDC) to a maximum of \$250.00 per month per family, no matter how large the family. If a limitation on public support for potentially healthy children is the law of the land, surely there will be restrictions on public support for children with severe genetic disorders.

WRONGFUL BIRTH, WRONGFUL LIFE

A variety of bacteria, viruses, chemicals, and other agents (and now, AIDS) are harmful to the fetus and the newborn. The reduction in neonatal gonorrheal ophthalmia and syphilis was due, in part, to litigation, which employed concepts from contract, negligence, and battery law, all of which formed the basis for the common law of malpractice. The improvement of contraceptive procedures and of methods for prenatal and postnatal genetic diagnosis induced the courts to make these discoveries available (within limits), and sanctioned liability.

In a wrongful birth action, the physician or another person or organization is sued by the parent for failure to prevent the birth of an unwanted child, or to

prevent the birth of a child with a genetic or other disease. In a wrongful life action, the child or the parent sues (on behalf of the child) and claims that the child would have been better off by not having been born [15,16]. But this allegation has serious problems. Tedeschi [17] pointed out that the act of the parent which the child claims injured him or her is the very act for which the child would not exist: The child that would be born would not be the plaintiff.

I will concentrate on the arguments of Shaw [18] on wrongful birth and wrongful life, because her contentions could indicate the future direction of human genetics policy. Shaw argued that the right to reproduce is not absolute, and cited state prohibitions against certain types of marriage. But Shaw went further and asserted that genes—like infectious agents—are transmissible units, and that the law can impose quarantine and compulsory vaccination in order to control communicable diseases. Comparisons were offered between genetic and infectious diseases: Both are transmitted to others; both vary in their rate of “contagion;” both are unequally distributed among populations; and both vary in morbidity and mortality.

PRENATAL NEGLIGENCE

Shaw argued that since recovery for fetal injuries is legal, children may sue their parents for prenatal injury. Shaw indicated that in most situations the defendant would be the mother, because the mother is the only one who has direct control over the fetus. Thus, negligent exposure to noxious chemicals, drugs, refusal to accept genetic counseling and prenatal diagnosis, refusal of prenatal therapy, or failure to take a modified diet for phenylketonuria could be the basis for action. *Smith v. Brennan* was cited in defense of this position: “The child has a legal right to begin life with a sound mind and body.” In other words, the child’s right to a healthy life takes priority over the right to reproduce. Shaw used as precedence child-abuse statutes. She would compel parents and prospective parents to enter alcohol and drug rehabilitation programs that would take custody of the fetus to prevent mental and physical harm.

COURT-ORDERED OBSTETRICAL INTERVENTION

In a national survey, Kolder, et al. [20] investigated decisions in court-ordered obstetrical procedures in which women refused therapy necessary for the survival of the fetus. Among 21 cases in which court orders were sought, orders were obtained in 86%. Eighty-one percent of the women were black,

Hispanic, or Asian; 44% were unmarried; and 24% did not speak English as their primary language. All the women were tested in a teaching hospital or were on public assistance. Forty-six percent of the heads of fellowship programs in maternal-fetal medicine thought that women who refused medical advice and endangered the life of the fetus should be detained. The authors concluded that court-ordered obstetrical procedures represented a growing problem, and that such policies were dubious.

Annas [21] argued that the right of privacy is inviolate to such an extent that a pregnant woman has a right to refuse surgery for the sake of her fetus. In a comment on the article of Kolder, et al. [20], Annas contended that the best chance to protect the fetus is through enhancing the status of all women by fostering reasonable pay for the work they do, providing equal employment opportunities and day care, according a reasonable social safety net, and ensuring all women access to high-quality prenatal services.

Andrews [22] suggested that the fetus evolved through the years from an entity perceived only through the visible expansion of the mother's abdomen to a view that fetuses are full members of society, with all of the rights and privileges. Andrews maintained also that the right to bodily integrity has been a stalwart of our society and asked, "Is it just to force a woman to undergo surgery to potentially benefit the fetus when we don't require a father to donate a kidney or even to donate blood to his existing child?"

STIGMATIZATION OF THE IMPERFECT

Some of the stereotypic attitudes and myths about disabled persons, and how these attitudes influence parents and physicians in the decision-making process about abortion, were introduced by Saxton [23]. Saxton has a neural tube defect with moderate disability, and wore leg braces until she was 12 years old. At 32, she has a slight limp. In order to urinate, she must catheterize herself three or four times a day. This can be done in any rest room, and takes about as long as it would take another woman to urinate. She is married and plans to have a child.

Saxton supported the pro-choice position on abortion, but rejected ending the life of a fetus for no reason other than it will be disabled. She believes that a "choice" means that individuals should understand the options and the opportunity for flexible decision-making and make an assessment based on their resources. Saxton stated that we live in a culture that is obsessed with health, well-being, self-reliance, athletic prowess, and rigid standards of beauty. The

disabled person is looked upon by the able-bodied world from attitudes of pity, to resentment, to low expectations. Particularly vexing is a common assumption that disabled persons are asexual. This is especially hurtful to disabled women because many consider parenthood; however, the medical community is not very sympathetic and is unaware of support for such women. Saxton's comments should be read in full. This is a poignant quote from her paper:

It is clear to me that the most painful and scarring parts of growing up disabled were the unnecessarily frightening separations from my parents when I was hospitalized in a charity hospital, and the patronizing, pitying and invalidating remarks from others. Having a body with physical limitations is a snap compared with dealing with these limitations. The oppression . . . is what's disabling about disability.

Perhaps we can learn compassion from the inhabitants of a poor village in the Cameroon. Several years ago, I visited this village and saw a well-dressed, clean, well-nourished child of about 12 who was sitting under a tree. He had what was probably a severe cerebral palsy syndrome. I stated that I thought that children as severely affected as this child would have been killed long ago. I was gently informed by my friend Professor Kaptue-Noche that this poor village and others like it considered the care of disabled children a community responsibility. I often think of the child and the African village when I am confronted with our perennial rejection of those whom we label imperfect. If a society is best judged by how it treats its most disadvantaged members, perhaps we are underdeveloped—a pejorative term we employ for African societies like this one in the Cameroon.

Further, in our rush to raise money for genetic and other disorders, we overlook frequently the potential effect of our propaganda on those we profess to help. Within the past five years, a prominent, private, national genetic organization had a fund-raising advertisement on television. A 12-year-old child appeared on the screen, begging for funds. He stated, and I paraphrase, "Please give, I will be dead before I am 20." My only thought was of the children with the disorder who saw this callous advertisement.

A EUGENICS CAUTION

There is a long-standing eugenics streak in the United States. Educators, philosophers, physicians, psychologists, geneticists, anthropologists, historians, the courts, legislators, and others supported persecution, sterilization, and incarceration of a wide assortment of individuals who were "different"—particularly those who were poor—since the rediscovery of genetics in the early part of this century. In fact, if there was no opposition to abortion in the United States, it is likely that our eugenics laws would be even more oppressive. We must be vigilant to ensure that eugenicists will not employ their monistic prejudices as a license to pursue their perennial goal of "eliminating the unfit."

A human geneticist, who defended patients with genetic disorders and was an outspoken opponent of eugenics, was the late Professor Lionel S. Penrose, who, ironically, was the Galton Professor at University College in London. When Penrose became Galton Professor, he also became editor of the *Annals of Eugenics*, and much to the consternation of many human geneticists, he renamed the *Annals of Eugenics* to the *Annals of Human Genetics*. Kevles [24] succinctly summed up Penrose's disdain for eugenics:

. . . According to some "our true destiny must be to try to produce perfect genes, regardless of personal interests" It is ultimately a matter of opinion . . . but for myself, I would rather live in a genetically imperfect society which preserves human standards of life than in one in which technological standards were paramount and heredity perfect.

NEWBORN SCREENING

All states and the District of Columbia have newborn genetic screening programs. At least 48 states have legislative statutes; the remainder have regulations provided by the Department of Health. All states now screen for phenylketonuria and hypothyroidism; 37 screen for galactosemia, 22 for maple syrup urine disease, 21 for homocystinuria, and 9 for biotinidase deficiency (Meany, personal communication, 1989).

Andrews [25,26] outlined the capricious nature of informed consent in some of these newborn screening programs. The District of Columbia, Maryland, Wisconsin, and Wyoming were the only jurisdictions to stipulate that parents

be informed and that they may object to the procedure. Even though it was acknowledged that education and counseling were crucial to genetic screening programs, only 13 states required counseling, and only a minority of the states provided for education of the public, the profession, or both.

THE MYTHOLOGY OF COMMON VALUES

It is often argued that our society's problems stem from a retreat from common values. Such lofty clichés ignore our history of genocide against Native Americans, slavery, lynching, racism, and segregation. Should we retreat to these societal values? The mythology of common values or a shared moral view was recently argued in Great Britain. Lord Devlin stated that a shared moral view is the cement that binds society in his objections to the Warnock committee reports [27], which upheld in vitro fertilization and surrogate motherhood—under certain conditions. Lord Devlin argued that the law could not permit acts that contravened shared morality. In opposition, Warnock argued that a “common morality” is a myth. Yet, the sanctity of a common morality is often used as a foundation for determining public policy.

But what is public policy? Someone once said that public policy is merely what those who have power decide. Even morality has been placed in this category. Variations of this thesis are ancient. In Book I of Plato's *Republic* [28], the sophist, Thrasymachus, maintained that laws serve only to protect the interest of those in power. A Marxist view [29] is that morality is contrived and dictated by the ruling elite to control the masses: All morality is class morality. Scholars of the critical legal issues movement [30] profess that the law is not neutral, but is guided and dictated by political considerations. These are caustic statements, but if the poor are to extricate themselves from mediocre health care in a society that encourages—and even mandates—participation in genetic programs, they must not allow themselves to be victims of mythology. The interests of the poor may not be what those in power—or this conference—may decide is the common good. If so, autonomy and pluralism are the best rejoinders to the exhortations of monistic religious, political, ethical, community, or genetic pressure groups.

ECONOMICS OF CLINICAL GENETICS SERVICES

Pyeritz, et al. [31], Bernhardt, et al. [32], and Bernhardt and Pyeritz [33] examined the economics of genetic services. In the first of the series of articles,

the authors cited a most important quotation from L. R. Dice in his presidential address to the American Society of Human Genetics in 1952: "It will rarely be practical for an heredity clinic to charge fees for its services. . . . an heredity clinic cannot usually be self-supporting." Pyeritz et al. [31] pointed out that improvement in clinical genetic services "requires a sensitivity to the special problems of all the major participants in genetic services: the providers, the patients and their families, and the payers [society]." In a time-analysis of a clinical genetic service, Bernhardt et al. [32] found that income from clinical practice covered 37% of the clinical portion of personnel costs, and that cognitive clinical genetic services are labor intensive, yield low payments per service hour, and are not financially self-supporting. To improve the economic status of genetic clinics, it was suggested that administrators should increase charges for services, bill for all services provided to family members, bill for all genetics professionals, including counselors and social workers, and even request payment at the time of service. Bernhardt and Pyeritz [33] expanded on the deficiencies of costs and added the necessity of seeking state, federal, and foundation support for services. A perennial problem, to which Dr. R. Stephen Amato and others can speak with expertise, is that there is no current procedural terminology (CPT) code specifically for genetic counseling, and third-party payers may not reimburse for the service. Often, medical assistance and crippled children's programs do not reimburse for genetic counseling, and insurance companies reimburse at a lower rate for counseling than for other genetic services, such as laboratory tests.

INSURANCE COMPANIES

Once it becomes known that many severe genetic disorders are preventable, insurance companies will ensure that appropriate tests and action be taken to restrain the birth of affected children. In fact, this has already come to pass. In the early days of the sickle hemoglobin screening programs, about one-half of all insurance companies increased their rates as much as 25% on persons who were carriers of sickle hemoglobin [6] under the spurious belief that such individuals had a decreased life expectancy.

GENETICS AND HEALTH PRIORITIES

The poor are susceptible targets. We have seen that the courts—in their endorsement of social eugenics—have upheld the sterilization of women who are

on welfare (*Dandridge v. Williams* [14]) after they have had a certain number of children. Accordingly, the courts may coerce poor women from having children with predictable severe genetic disorders, because children with genetic diseases cost the state far more than do healthy children.

Genetics programs are but one facet of a multiplicity of interacting health issues. In the United States, for example, genetics programs in blacks, Hispanics, Native Americans, Asians, poor whites, and other discriminated and disadvantaged groups must coincide with efforts to relieve poverty, foster quality education, stimulate employment, support access to quality health care, and all of the other benefits that the more affluent members of the wealthiest country in the world enjoy.

On the other hand, prenatal diagnosis for a large number of genetic disorders creates a myriad of problems, particularly for persons with sickle hemoglobin. Newborn screening for sickle cell disease saves lives, but screening of pregnant women for sickle hemoglobin also ameliorates morbidity and mortality, for women will be detected who do not know that they have sickle cell disease. Consequently, mandatory screening programs for black pregnant women could be legislated under the guise of saving lives. (This has already been suggested in high-risk AIDS communities to decrease the incidence of newborns with AIDS.) And women who are at risk for having a child with cystic fibrosis could be the next targets when carrier and disease screening is perfected by DNA analysis. Unlikely? No. There is an old aphorism, "One can never do one thing." State mandatory screening programs for black children, adults, and premarital partners for sickle hemoglobin were instituted in the 1970s—at the instigation of the black community—with far less justification [6]. Accordingly, the recent landmark acceptance of *mandatory screening of newborns for sickle cell disease* by a National Institutes of Health Consensus Conference in 1987 opened the door for mandatory prenatal screening of pregnant women, because sickle cell disease begins in utero, not at birth. Admittedly, newborn screening for sickle cell disease should lead to a decrease in morbidity and mortality for infants with sickle cell disease. And reduction of illness and death are the principal goals of health care, but we cannot stop here. Community education and genetic counseling of parents of affected children must be ensconced in any newborn screening program, and this does not mean *selective education and counseling*. *The option of prenatal diagnosis and selective abortion of affected fetuses for future pregnancies must be presented.*

Unfortunately, the pro-life movement has bludgeoned geneticists, scientists, physicians, and other health care workers who are interested in making genetic services available to all to such an extent that many of them carefully disclaim what should be indisputable: Human life begins at conception. Unfortunately, this collective amnesia is because federal, state, and many privately supported organizations and scientists will have a sword of Damocles hanging over their programs if this basic fact is admitted.

PUBLIC ACCESS TO GENETIC TECHNOLOGY: A POSSIBLE SCENARIO

- With the exception of a few digressions, each technological advance in sterilization, contraception, abortion, genetic carrier identification, genetic therapy, or prophylaxis has been followed by general public acceptance—even though some individuals might be outraged.
- Although the courts may have been reluctant in certain instances of wrongful life, they have exercised the common law of malpractice to ensure that physicians and other health workers make available to their patients recent advances in health technology, including the prevention of the birth of children with genetic defects.
- Once it becomes general knowledge that the birth of children with certain severe genetic disorders are preventable, other members of the family and the community may question the wisdom of ignoring medical advances.
- It is inconceivable that insurance companies will countenance the proliferation of the birth of children with severe preventable genetic disorders, without imposing prohibitive costs on the family. Accordingly, insurance companies will exert pressure to utilize genetic technology.
- As more and more women enter the marketplace, family sizes are decreasing to such an extent that in the middle and upper income groups the number of children is below the replacement level. Women who have fewer children will want to ensure—if at all possible—that their children will have a reasonable chance of being healthy. This is particularly true of the large numbers of working women who have their first child after 30 years of age.

GUIDELINES

The following guidelines are proposed:

- Develop procedures for the equitable use of genetic technology by all who wish to participate—on a voluntary basis. Our affluent society must not accept the shibboleth that health care resources are scarce.
- Construct plans for the replacement of state mandatory genetic programs by voluntary genetics legislation, modeled on the states that already have successful voluntary programs.

I realize that the latter suggestion is most unpopular; however, such a policy could be urgent, because if it is not instituted, mandatory prenatal screening programs could be instituted for women who are at risk for having a child with sickle cell disease, thalassemia, cystic fibrosis, Tay-Sachs disease, or Down syndrome, with far more economic and health justification than mandatory testing of newborns for low frequency phenylketonuria, hypothyroidism, biotinidase deficiency, and galactosemia.

Even so, I hope that freedom to choose is the preeminent public policy. We must defend and support women who do not wish to have children with severe genetic disorders, and elect prenatal diagnosis and abortion. On the other hand, we must allocate health care resources to those families who eschew abortion and elect to have children with severe genetic disorders, because a society that mandates perfection fertilizes mischief.

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RESPONSES TO THE KEYNOTE ADDRESS

JANE S. LIN-FU, M.D.

I am delighted to participate in this important National Symposium on Genetic Services for Underserved Populations. Dr. Bowman has brilliantly covered the key issues that need to be addressed at this symposium in his keynote presentation. In my response, I would like to reemphasize certain points he made, raise some new issues, and add an expanded perspective on others.

EQUAL ACCESS TO SERVICES WITH EQUAL PROTECTION OF RIGHTS

The underserved populations could also be defined as the most vulnerable populations in our society. They include the poor, the racial and ethnic minorities, and the new Americans (new immigrants and refugees). They are viewed by many as people who are incapable of fully realizing the American dream, people who are outside of mainstream America. They are also people who have little or no voice in society.

In our attempt to provide access to genetic and other health services for these underserved populations, we need to assure equal protection of their human rights at all times, lest in the name of providing opportunity and access to genetic services, we deprive our fellow human beings of their very basic rights and those of freedom of choice in our democratic society. We need to make the careful distinction between mandatory availability of genetic tests to all who want to be tested, and mandatory testing of all—with or without their consent, or despite their dissent.

PREVENTION OF GENETIC DISEASES VERSUS PREVENTION OF MORBIDITIES OF GENETIC DISEASES

It is crucial to recognize a very fundamental difference between the prevention of diseases and the prevention of morbidities of diseases. For most diseases, the need for primary prevention is unequivocal. We would rarely dispute the

need to prevent cancer, coronary heart disease, arthritis, kidney stones, or infectious diseases such as polio, measles and AIDS. But, we need to take heed not to simplistically apply the same concept of prevention to genetic disorders.

Three decades ago when the principles of preventive medicine were first broadly applied to some genetic disorders, the effort involved the prevention of morbidities of the diseases, for example, mental retardation and other handicaps resulting from untreated phenylketonuria (PKU), maple syrup urine diseases, and galactosemia. As technological advances made possible prenatal diagnosis of some genetic disorders, the application of the concepts of preventive medicine suddenly seems to have been extended from the prevention of morbidities of genetic diseases to the prevention of the diseases themselves. Insufficient thought has been given to the critical difference between the implication of attempting to prevent genetic disorders and efforts to prevent other diseases. Thus far, in few other diseases does prevention involve the taking away of life through abortion, or the prevention of life through refraining from conception. Health professionals offering genetic counseling and education need to bear in mind this important distinction, and recognize the grave difference between primary and secondary prevention in genetics. It is inappropriate and dangerous to use the approach taken toward the prevention of other diseases and apply it to genetic services. Moreover, since the purpose of genetic counseling and education is to inform persons at risk of the nature of the disorder, the risk of occurrence, and the options available, and *not* to tell them what to do, the effectiveness of genetic programs should be measured differently from that for other types of health education. Health administrators should therefore take caution in applying the formula of cost-benefit analysis used for other diseases in genetic programs.

ETHNOCULTURAL BARRIERS: DETERRENTS TO GENETIC SERVICES FOR ALL, NOT SOME, MINORITIES

Among the many deterrents to access of the underserved populations to genetic services, ethnocultural barriers are probably among the most important. Our health care system itself is one of the least recognized and least visible aspect of these barriers. Few health professionals realize that the health care system is a cultural system that has been shaped by mainstream America to meet its perceived needs. Racial and ethnic minorities have had little input in

designing the system. In 1988, blacks accounted for only 6% of the medical school admissions even though they made up 12% of the U.S. population.

In addition to minorities, new immigrants and refugees, the so-called new Americans, regardless of race and ethnic background, are also confronted with severe ethnocultural barriers to health services. In fiscal year 1988 alone, 643,025 legal immigrants were admitted into the United States. Latin America and Asia now account for the vast majority of immigrants, each contributing over 40% in the last few years. In addition to legal immigrants, close to one million refugees from different parts of the world have been resettled in the United States in the last decade.

At both the institutional and personal level, ethnocultural barriers caused by insensitivity of both the health care system and health professionals have been pervasive. Many health professionals naively view ethnocultural barriers as a one-sided problem. To them, the barriers exist because the service consumers do not speak English, do not understand the U.S. health care system and Western concept of diseases, or do not hold the mainstream cultural values and standards of behavior. These health professionals fail to see that their own insensitivity to the special needs of minorities and new Americans plays a critical role in creating the barriers. In short, they do not see themselves as an important part of the barriers. In the last decade, the sudden explosion of close to a million refugees from Southeast Asia and rapid expansion of the Hispanic population on the American horizon caught the U.S. health care system quite unprepared to serve these minority populations that are culturally distinct from mainstream America.

In our attempt to be culturally sensitive, it is important not to apply stereotypes, that is, to assume that all persons of a racial or ethnic background are the same. I wonder if the omission of Asian-Pacific Americans from the list of "discriminated and disadvantaged groups" in Dr. Bowman's keynote address is not related to the common stereotype of Asian Americans as a "model minority." The media is full of success stories of Asian Americans. This has created the devastating positive stereotype, based on the erroneous assumption that all Asian Americans have succeeded through hard work and self-reliance, and have neither needs nor problems. Many assume that Asian Americans have no need for affirmative action in order to gain equality in the American society. Nothing can be further from the truth for most Southeast Asian refugees and new immigrants from Asia. They are disadvantaged and discriminated against.

They have poor health, live in poverty, and cannot find employment, like many other racial and ethnic minorities.

In the last decade, Southeast Asians accounted for three quarters of all refugees resettled in the United States. From 1981 to 1985, persons from Asia made up 48% of legal immigrants admitted. These new Asian Americans have a high prevalence of genetic disorders such as thalassemia, hemoglobin E and glucose-6-phosphate dehydrogenase deficiency (G6PD). It is critical that health professionals recognize that for this population, as for all other minorities, ethnocultural barriers are serious deterrents to the use of genetic services.

PUBLIC PARTICIPATION IN PUBLIC POLICY

The recombinant DNA technology has ushered in a new era in which public and corporate policies on genetic testing for future and potential diseases may be made in the not-too-distant future. When such policies come into existence, their impact on employment, health and life insurance, adoption, and other aspects of one's personal life could conceivably be devastating if the freedom of choice to undertake genetic testing is not safeguarded. Pre-employment testing for predisposition to diseases such as coronary heart disease or certain cancers may lead to employment discrimination.

Likewise, identification of certain heterozygous carriers of diseases, particularly if both spouses are at risk, may present a problem in health insurance since children are covered by their parents' insurance plans. How can the public play a role in shaping such policies when they are made in order to protect and safeguard the most vulnerable populations in our society? The people who are currently underserved by genetic services may become overserved in the future, not because they desire such services, but because public policies were made with no input from those with no voice in our society.

F. JOHN MEANEY, PH.D.

In his stimulating address, Dr. Bowman raises several important issues that are critical to the goals and objectives of this conference. Among those Dr. Bowman discussed, I view the following as the most crucial to our deliberations over the next few days:

- 1) The worsening situation for the poor in our country and how this impacts on genetic services;
- 2) the dilemma created by conflicting goals, that is, the goal of preventing genetic diseases versus the goal of providing medical and social support for those with genetic diseases;
- 3) voluntary versus mandatory genetic service programs;
- 4) the role of genetic service programs in the total health care scheme, especially for the poor, in this time of diminishing financial resources for these services; and
- 5) public access to and use of genetic technology, and how this will evolve as future technologic breakthroughs are translated into medical practice.

We will now cover each of the issues in greater depth.

Dr. Bowman raises the first issue concerning the plight of the poor with the upsetting statistics on infant mortality, maternal mortality, and teenage pregnancy. It is even more disturbing when one realizes that these same kinds of statistics were presented some 20 years ago in a hard-hitting book entitled *Disadvantaged Children* by Herbert Birch and Joan Gussow. The point is that we have not come very far in 20 years and even seem to be regressing. We write a lot about these statistics, but the improvement is not yet there and health care for the poor is still a major cause for concern by all of us in this nation of plenty. Unfortunately, we have not found solutions that are acceptable to the key players.

In recent years, there has been increasing media attention to the problems of infant mortality and teenage pregnancy, yet this has not translated into a concerted call for change. What has happened in the public health arena in response to media attention is that competition for already scarce funds for services has increased, and genetic services are not often given much priority in the total scheme.

In his paper, Dr. Bowman deals with the dilemma of preventing genetic diseases, by reminding us of the language used in the various pieces of federal legislation that led to the genetic service programs we have today. The primary goal was prevention, yet some of the methods for prevention are unacceptable to some people, as we know all too well from the controversies and confrontations of the past few years. This goal also sends a mixed message to individuals with genetic diseases and to their families concerning how we, as health care professionals, really feel about their presence on this planet. Dr. Bowman treats this matter candidly by presenting the views of Ms. Saxton, an individual with moderate disability as a result of a neural tube defect. Ms. Saxton's expressed views on pregnancy termination demonstrate all too well how complicated the issue is, and how variable the views of individuals can be.

The third key issue is mandatory versus voluntary programs regarding genetic services. This is a critical issue in the public health genetics arena. Dr. Bowman seems to support voluntary programs across the board. He proposes two guidelines: 1) That the means be developed for genetic technology to be used equitably by everyone who wishes to use these services on a voluntary basis, and 2) that planning be taken for the replacement of mandatory state genetic service programs by new legislation that reflects a voluntary basis for participation. He suggests further that the latter be modeled on states that currently have successful voluntary programs. Although I would agree with the first proposal, I have to state that if by "state genetics programs" Dr. Bowman is including newborn screening, then I am in disagreement with his second proposal. I think newborn screening programs are a special case. The primary goal of these programs, traditionally, has been prevention of mental retardation in individuals with conditions such as phenylketonuria. All but two states have laws that do not use the voluntary model. The track record is that state legislatures usually have seen fit to pass laws mandating screening, and in many cases allow parents to opt not to have screening done if their religious values preclude such testing.

I think there is a good reason for the legislation that does not use a voluntary model—it ensures in an imperfect world, with limited resources in many state health departments to monitor the screening process, that few newborns will slip through the cracks and not be screened. State newborn screening programs have been some of the most successful public health programs in genetics. Changing state laws, I think, would invite problems unless resources were

made available to health departments to provide continuous training of the hospital staff who are involved directly with the parents of newborns about the screening programs.

Issue number four in my list concerns the role of genetic service programs in the overall health care scene, especially public health genetic programs targeting the poor as an underserved group. The continuation of genetic services in public health is strongly tied to the funding of state maternal and child health programs. As Dr. Bowman points out, several studies have demonstrated statistically that genetic counseling services (cognitive services) are not financially self-supporting. Thus, other sources of financial support, such as MCH Block Grant funds, are sought by centers to provide services for families who cannot afford to pay. These programs must be continued, and, as Dr. Bowman suggests, they must be incorporated into the total health programs that target the poor, and/or ethnic minorities as underserved populations. Dr. Bowman also stresses that such programs must be sensitive to the social, economic, and health factors (and, I would add, cultural factors), which exist in poor communities and in minority communities, or, as he puts it, the programs "will have almost no prospect for success." I suggest that we can begin by providing appropriate exposure to these issues in our medical schools, our clinical genetics training programs, and our training programs for genetic counselors. Dr. Rayna Rapp, a medical anthropologist in New York, recently reported her research on genetic counseling in the New York City area. She states that, "According to the counselors I have interviewed . . . there is not much discussion [in training programs] of the cultural constraints and resources with which different pregnant women and their families may be operating" [1]. There is work to be done in this area.

I am reminded of an event that occurred in New Zealand while I was teaching there. The students at the University of Auckland Medical School had spent time in a Maori village, and invited Maori elders to pay a visit to the medical school. As many of you know, the Maori are the indigenous Polynesian people of New Zealand. During an entire weekend, the students ate, talked, and camped with the Maori people in rooms at the medical school. The medical school was later designated by the Maori as a Marae, a place of special religious significance, and therefore acceptable as a place for medical care and healing. Perhaps our medical schools should be turned into similar places of acceptance, rather than places, as we so often hear, "where one goes to die."

The fifth and final issue in my listing is concerned with public access to developing genetic technology as it is placed in medical practice. Dr. Bowman speaks of the inevitability of increased usage of genetic technology since public acceptance usually has followed each new technologic advance, and communities also begin to question ignoring methods that lead to the prevention of genetic diseases. He also acknowledges the legal system, insurance companies, and family demographics as additional driving forces behind the acceptance of new technology in genetics.

I think we can easily question the inevitability of public acceptance of advances in genetic technology if we consider the questions raised in recent years about nuclear technology and space exploration, and the questions that are being raised in recent weeks about what we humans are and have been doing to our environment. It does not follow that the public will accept all of what is coming in the years ahead concerning applications of genetics to human disease. If we have learned to question other modern technologic advances—usually as a result of some disaster involving those technologies—then we can envision a similar scenario with respect to genetic technologic advances if we are careless and move ahead without paying attention to potential problems with the technology and its application. The public is probably even more wary of genetics than it was of the nuclear and space technologies before Three Mile Island and the space shuttle disaster opened our eyes to the dangers involved.

In thinking about the inevitable advance of genetic technology and its consequences for human existence, I am reminded of another incident I observed in Auckland, as I walked to the bus stop one evening after a full day at the university. As I pushed up the hill toward my destination, I could hear a young man shouting as he came up behind me. He had obviously visited a number of pubs and he was shouting, "I'm a train, I'm a bloody train." As he grew closer, I could see ahead of us a Kiwi construction worker (a "she'll be right, mate" character) in a doorway eyeing this young fellow as he approached. Just before he got to the doorway, the young man again shouted his identity as "a train," to which the Kiwi worker replied, "Good on ya, but are ya on time?"

The young man, as he pushed up the hill, gloriously declaring his identity, is, perhaps, analogous to our advancing genetics technology. The young man is inevitably going to reach the top of the hill, just as geneticists are going to sequence the entire human genome. But, are we "on time," as the questioning Kiwi asked? Do we care enough to understand the consequences of advancing

technology? What sort of world will it be when humans have a greater opportunity to know some of their future through their genes? These are difficult questions, but we need to be seeking the answers now, because the time is approaching for the genetics "train" to reach the top of the hill.

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KERMIT B. NASH, PH.D.

Dr. Bowman's presentation on genetic services for underserved populations provides an excellent base for understanding the problems of the underserved populations. I have not repeated the word "genetic" in this discussion because the focus in this response will be the multiple reality factors that comprise the term "underserved." All too often professionals transpose the underserved to this spelling, the "undeserved."

Some of the sobering statistics presented by Dr. Bowman demonstrate that public policy for health and social services has disproportionately affected poor and minority groups in the United States. Health programs enacted to address the needs of the poor and minority population are often ineffective because of misapplications, restrictive eligibilities, inadequate support services, and hostile or indifferent attitudes of the assigned "helping professionals."

Poor and minority families face a dual threat to their health. Poverty, unsafe housing, and poor nutrition make illness much more probable for these families, who at the same time have less access to competent health care and information.

The attitudes of providers of services often constitute a barrier which requires that the potential client trade in his/her dignity, privacy, and feelings of competency in return for services from an institution. The underserved and non-served have limited access to suitable housing, jobs, education, training, medical,

and information services. They are underserved in every area of life, including genetic information. It is doubtful, given a choice, that the latter would earn a high priority over a job, decent housing, and adequate education needed to survive in this increasingly technical society.

Dr. Bowman has clearly articulated how the increase in technical developments has changed the medical genetic field. The cover story in the March 20, 1989 issue of *TIME*, "The Gene Hunt," describes the three billion dollar project in process to map the chromosomes and decipher the complete instructions for making a human being. The article states, "The very thought of being able to read the entire genetic message and perhaps alter it is alarming to those who fear the knowledge could create many moral and ethical problems." It continues by listing questions: "Does genetic testing constitute an invasion of privacy?"; "Could it lead to more abortions, to discrimination against the genetically unfit?"; and "Should gene therapy be used only for treating disease or also for *improving* a person's genetic legacy?" For those attending this symposium who share a genuine concern regarding such questions, and for the underserved, the non-white, and the poor who are the underserved, the next statement is chilling: "Although scientists share many of these concerns, the concept of deciphering the human genome sends most of them into paroxysms of rapture."

In the United States, the need for all support services remains higher among blacks, Hispanics, Native Americans, and poor Americans. In the 1980s, available jobs demand well-educated, technologically competent workers. Many funding mechanisms were eliminated in the 1980s and many more reduced to a non-functioning level. The stripping of resources from the poor is being continued by the present administration:

- 1) The minimum wage will remain at \$4.25 an hour while food prices and housing continue to escalate. Jobs that can be held with less than a high school education are disappearing.
- 2) Demand for skilled, better educated, technologically competent workers prevails.

Dr. Bowman's careful overview of maternal-mortality, out-of-wedlock births, and inadequate health services underscores the urgent need to place the plight of the "underserved" on both the national and local agendas as a priority for action. It is evident that the highly educated, the economically able and the non-blacks, non-browns have the power to make the decisions—what knowl-

edge shall be acquired, what research shall be done, who will be used for study. The chance to spend millions on genome research in lieu of providing good medical services, decent housing, adequate education, and employment opportunities, is reflective of the kind of society we have in the 1980s and 1990s.

Dr. Bowman's well documented paper raises serious questions concerning the survival of the underserved populations and their potential for a more equitable lifestyle as an expectation in a democracy. How can this David of the underserved compete with the Goliath of power held by the well served?

The answers and approaches must be multifaceted. Perhaps some of the following should be considered:

- 1) More accurate information dispersed in an appropriate form that can be used by the underserved is an obvious need.
- 2) Training in the critical analysis of information should be available to children from kindergarten level throughout the school system.
- 3) Training in communication and participation in how to pressure the body politic should be considered as a part of the effort to increase the power of the underserved.

The usual approaches of so-called "community-education" as we have known it in the 1960s, 1970s, and early 1980s, is no longer viable in the late 1980s and beyond. Meetings held in housing projects and centers, clinics and schools are not well attended. The fear of crime and the pervasiveness of drugs have altered the way information and behavioral changes for action can be affected. I do not know how the underserved can be mobilized to gain and control more areas of their lives. But I do know that a kaleidoscope of solutions must be sought to stem the tide of possibilities that powerlessness can unleash. As the technical skills to alter life forms increase, I suggest that we all take a serious view of the grim, but realistic, presentation Dr. Bowman has given us.

This serious view will require a plan for interventions. A suggested form of reference includes four major interventions:

- 1) Political-economic;
- 2) Legislative;
- 3) Humanistic (social); and
- 4) Empowerment.

I would like to comment that the institutions and organizations which serve poor families have an ethical responsibility to determine whether their structure, their philosophy, and their practices are in conflict with the basic needs of their clientele. Individual workers should receive specific training and guidelines devoted to eliminating the commonly misperceived correlation between family status and its ethnicity. However, dramatic institutional changes will occur only when agencies integrate their policy, administration, and service structure to the extent that the poor are fully represented at every level of decision making, be it in the board or the waiting room.

Social workers, health educators, and other practitioners are the instruments of public policy. They implement programs and policy directives with relatively little voice in their formulation and even less of a role in deciding their long range consequences. At the cutting edge of policy, these professional workers should examine their personal and organizational attitudes toward poor clients. If any prejudgment based on class or ethnicity does occur, then that worker must modify his/her own behavior and then work to reform the policies that promote and perpetuate such roles.

In conclusion, Dr. Bowman's presentation is reminiscent of a song written in the early 1970s by colleagues of mine:

NEW OLD BLUES

The Stay Sicker, Die Quicker, Can't Get No Health Care Blues

I got the stay sicker, die quicker, can't get no health care blues.
 Yes, I got the stay sicker, die quicker, can't get no health care blues.
 And let me tell you—people, that's really some bad, bad news.

The old folk used to tell me, "Son, money can't buy health.
 You can't stretch out your lifetime with riches or wealth."

I tried hard to believe them, but soon began to see
 The poor folk all around me are sick as they can be.

They got the stay sicker, die quicker, can't get no health care blues.
 And I'm here to tell you it's some bad, bad news.

I go to the clinic, the first thing they ask
Is my Medicaid number, or I just don't get past.

Now there's this ringing in my head,
my wife's sick in bed,
And yesterday they told me that my baby has lead.

I got the stay sicker, die quicker, can't get no health care blues
And I'm gonna' tell you, that's some bad, bad news.

I went to the doctor, though I felt pretty well;
He told me I got something that I can't even spell.

I asked him was he kidding, but he said it was no joke;
And if I didn't slow down, I just might have a stroke.

Now tell me how to slow down when every day's a fight;
And I'm working two jobs—got to work both day and night.

Troubles sneak up on me, it ain't too hard to see
There's little chance of being healthy when you're as poor as me.

You get the stay sicker, die quicker, can't get no health care blues;
And you know, people, that's really some bad, bad news.

You read in all the magazines about dieting and such;
But if you don't have some money, that sure don't help you much.

I wish someone would tell me just what I'm supposed to buy
When prices in my neighborhood are high enough to fly.

You better listen to me, cause I got a tale to tell.
If you don't have no money, there's little chance of keeping well.

There's things that folks don't tell you, there's facts that you don't see—
Like we don't hardly have much chance to live past sixty-three.

We got the stay sicker, die quicker, can't get no health care blues.
And if you don't know it, it's some bad, bad news.

These folks who go to meetings and sit around all day
Discussing poor folks' problems, hear what I've got to say.

They should live where I live, eat the food that I can buy.
They'd soon begin to understand and know the reason why

We got the stay sicker, die quicker, can't get no health care blues.
They'd know for sure that it's really some bad, bad news.

Lyrics: Naomi Chamberlain, Claire Hurst
Arrangement: Charles Blackwell
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GLENDIA PURDIE HARRIS, M.S.A.

I concur with the closing recommendations of Dr. Bowman proposing that freedom of choice become preeminent public policy. I concur that we must support those who do not wish to have children with severe genetic disorders. But, I also agree that we must support those who eschew abortion and choose to have children with severe genetic disorders. Failure to support this choice could

result in a resurgence in the stigmatization of the imperfect and the handicapped in general. Consequently, abortion and selective sterilizations could be used as a means to support this philosophy.

Legal rulings continue to address these issues as demonstrated by the following cases. Therefore, we know that this issue is not dead. In 1984 the Saxton case, as highlighted by Dr. Bowman, dealt with some of the stereotypic attitudes and myths about disabled persons and how these attitudes influence parents and physicians in the decision-making process about abortion. Saxton supported the prochoice position on abortion, but rejected the issue of ending the life of a fetus for no other reason than it would be disabled [1].

In *re* Grady, 1985, the New Jersey Supreme Court, in addressing the issue of eugenic sterilization, found that:

It cannot be forgotten however, that public attention toward . . . the handicapped in general, ha[s] some times been very different. We must always remain mindful of the atrocities that people of our own century and culture have committed upon fellow humans. We cannot adequately express our abhorrence for the kind of ideology that assigns vastly differing values to the lives of human beings because of their innate group characteristics or personal handicaps [2].

One cannot assess the value of life based just on whether or not one is deemed "genetically perfect or imperfect." I believe that the quality of life is what one chooses to do with the capabilities that one is given. To deny this choice to one, simply because he or she is disabled, can have far reaching consequences. Therefore, we must vehemently oppose such schools of thought, and vigilantly seek to counter them whenever they appear.

Further evidence is found from a quotation in Dr. Bowman's paper, wherein Professor Lionel S. Penrose is defending a patient with a genetic disorder. "But for myself, I would rather live in a genetically imperfect society which preserves human standards of life than in one which technological standards were paramount and heredity perfect" [3].

As a patient with a genetic disorder—sickle cell anemia—I am indeed grateful for such commitment of ideals. I adamantly support those who choose to carry their children with genetic disorders to full term, although I realize that there are varying degrees of severity and quality of life. I still admire those

who do. I stand as a true testimony to the fact that one can achieve, do increasingly well, and be a contributing member of society, despite one's genetic impairments. Through a strong belief in God, family, and self, and with a supportive cadre of medical personnel, I have persevered despite painful and seemingly insurmountable odds at times.

On a humorous note, a failure to have allowed my birth would have robbed me, my parents, my community, and humanity as a whole, of the joys and sorrows of knowing Glenda Purdie Harris. However, I am not unique. There are perhaps millions of individuals like myself, who have persevered and now claim tremendous victories and successes in all walks of life, which modern medicine never deemed possible. Further, it is likely that many were poor and minorities, and tremendous resources were utilized to promote life. However, these successes make it all worthwhile.

The poor, regardless of race, deserve the best quality of health care, in spite of budget deficits and insufficient funding. Therefore, I adamantly support continued allocation of funding for research, education, testing, counseling, medical care, and medical support services for the underserved populations, especially the poor.

Our mission is therefore to increase utilization of existing services. Too often, services are in place, yet the underserved person fails to access these services. Perhaps this is due to an insensitivity on the part of the professional staff and a lack of advocacy on the part of the affected patients. Sometimes, the professional staff (physicians, nurses, social workers, and other allied health personnel) respond to the poor in a less sensitive manner than to those who are middle income and above, who are generally paying customers. As a child, I remember the cruel and insensitive manner with which my physician's nurse addressed my parents about the "bills" and their inability to pay the bills as rapidly as they occurred. We also suffered abuses because of my illness. Few people really understood the unpredictability and seriousness of my illness. They couldn't relate to my parent's grave concerns when my temperature spiked, or when I cried in severe pain with no relief from the medicines of childhood. My mother, as proud a black woman as I will ever know, always behaved admirably despite these humiliating situations. She told me later that she always placed the health care of her sick child first. This necessity always enabled her to remain calm and appreciative despite the insensitivities.

However, not all parents and patients are able to endure these and other situations that are demeaning and humiliating.

Another reason for underutilization may lie with cultural differences and a failure on the part of the poor, especially minorities, to accept these programs because they see them as "handouts." There are also misconceptions about the programs and who should use them. From my own pre-adulthood experiences, I remember my mother handling this issue differently, also. She utilized all channels available to receive assistance for her sick daughters with sickle cell anemia. This was necessary because we had a large family of eight children and my father had a low-salaried federal job. She learned to work the system. She utilized the free lunch program for both of her daughters. She utilized the Public Health Department's sick children and dental programs to supplement our health care in between illnesses. She also utilized the services of the March of Dimes when my sister suffered a severe stroke and needed braces to help her to walk again. When I was able to go to college, although she did not want me to leave home, she consulted with the Department of Vocational Rehabilitation to see if they could assist with my college tuition. Although I received two full academic scholarships, Vocational Rehabilitation provided for other college costs during my four years at school. I realize that most of the services I have mentioned relate to supplemental services, but I feel that collectively, they are all important. They all contribute to a patient having a more productive life.

From my experiences, I can attest to the need for patients to become more knowledgeable and access all available services. However, there are some drawbacks. I remember how my mother spent hours waiting in long lines at the Department of Social Services trying to secure help for her daughters. She also endured many disappointments because we were not eligible for many services, as a result of my father's employment. During my sister's period of enrollment in the transfusion program at Duke University Medical Center's Comprehensive Sickle Cell Program, I can remember the all-day trips to the clinics. I can remember these commitments to acquiring better health care. However, it seems that nothing in life is acquired without some inconvenience and sacrifice. Perhaps this is the message that we need to use in order to reach the underserved. They need to be made aware that there are a multitude of services available. The patient and/or the parent, however, must learn to access those services that he or she needs. Further, it must be made known that there

may be some inconveniences and sacrifices. In the end, the patient and/or parent must make a commitment to acquiring the best services available.

Further, during my recent studies for the Master of Science Degree in Administration, it was necessary that I examine the North Carolina Department of Human Resources' annual budget for the Genetic Diseases Program. My recommendations included the fact that there was a need for increased genetic counselors and case-management personnel with a subsequent increase in salaries. Some programs are understaffed and the underserved cannot adequately access them. This may be the reason for underutilization of these services. Let's make sure that adequate personnel are there to serve the underserved.

In conclusion, my recommendation is that we continue to provide genetic services and sufficient personnel to administer these programs. Further, in order to increase utilization by the underserved, I encourage patient self-advocacy. This is perhaps the most underutilized resource that is available to all patients. I strongly endorse the effectiveness of patient self-advocacy. During my childhood, my mother was always there. She inquired about treatment, prognosis, home care, and program services. As an adult, I have followed her leadership. In my successes and failures, I have always requested information, asked for referrals if not satisfied, read pertinent literature, and sought out professional personnel who were knowledgeable and sensitive to my disease. I also recommend a continued thirst for knowledge as it relates to one's illness. These tools have enabled me to access those services that are available for the patient with a genetic disease or any illness. The services are there, but often it is up to the patient or his/her family to access them.

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WORKSHOPS

A. THE EFFECTS OF ETHNOCULTURAL BACKGROUND ON ACCESS TO AND USE OF GENETIC SERVICES

HEALTH CARE CONCERNS OF HISPANIC POPULATIONS

MARY THORNGREN, M.S.

Welcome to the workshop on ethnocultural considerations. It is a pleasure to have the opportunity to speak with you today. The purpose of this "National Symposium on Genetic Services for Underserved Populations" is to identify existing services, promote access to and utilization of these services, identify gaps in services to underserved populations, and to provide recommendations for the development of new services and the delivery of services in a culturally relevant manner. According to Webster, *underserved* means "provided with inadequate services;" therefore our task is to discuss and develop strategies about how we can improve those inadequate services by reducing the barriers to care.

The specific workshop objectives are:

- 1) To identify the attitudes of various cultures to the use of genetic services;
- 2) To identify ethnocultural attitudes towards illness; and
- 3) To explore means by which providers can be trained to address ethnocultural considerations in the delivery of services.

As presenters, we will be proposing that we keep in mind the importance of addressing the overall health status of black and Hispanic populations, and delineating what barriers exist to preventive health care in general. We are proposing this slight deviation from our workshop agenda, because we are in the middle of a health care crisis in this country and black and Hispanic populations are disproportionately affected by this crisis. Ethnocultural issues—while extremely important—are only one of the barriers to care.

I will start by proposing the following:

STATEMENT OF THE PROBLEM

Underserved populations face greater barriers accessing basic preventive health care services and genetic services.

These barriers include:

- language gaps;
- misunderstandings arising from differences in cultural expectations, communication styles, and values;
- Hispanics' mistrust of the health care system born of repeated negative experiences;
- high medical costs;
- cultural and class stereotyping; and
- institutional policies that display insensitivity towards Hispanics.

These impediments were identified in a needs assessment that the National Coalition of Hispanic Health and Human Services Organizations did with health care providers across the country to identify the barriers to Hispanics seeking preventive care.

How then do we remove or ameliorate these barriers? There are two steps that I propose must guide all of our work.

STEP #1

We must start by defining our target audience very specifically. This sounds simple and perhaps even simplistic, but in my experience it is rarely the beginning point for any kind of discussion about delivering health care.

If it were, we would not be talking about underserved populations—everyone would be included in our service delivery system.

STEP #2

We acknowledge that we live in a pluralistic society—that everyone is not exactly the same—nor is that a desirable goal. One of the basic premises of American culture is that our country is a melting pot. We think of ourselves as being a homogeneous society and put a high value on sameness. The definition of homogeneity is “of the same or a similar kind of nature; to blend diverse elements into a uniform mixture.”

I would like to propose that this is a myth—we really are heterogeneous—“consisting of dissimilar or diverse ingredients which are mixed.” We are more like a stew in a pot—we may have a common gravy, if you will, but each of the ingredients is different. We may have melted together on the surface, but underneath we are shaped by strong cultural differences and uniquenesses.

If we accept that premise, and for the purposes of this session I would like to invite you to consider it, then the challenge we face daily is balancing our desire to value sameness and yet address existing differences realistically as we plan our service delivery systems.

WHO NEEDS CARE?

Let us go back for a moment to the barriers which I just mentioned and discuss each one of them in more detail:

Barrier 1: Language Gaps

Spanish is spoken in 5% of all homes in the United States. Although most Hispanics over age 18 can read English, many express a preference for speaking Spanish. In fact, a study of more than 2,000 Hispanics aged 18 and older in 21 markets across major U.S. regions (Strategy Research Corporation, Hispanic Market Study [1]) found that more than half of the respondents felt most comfortable speaking Spanish. Most providers speak primarily English, making communication challenging.

Language barriers can be overcome by:

- 1) Teaching providers the skills to deal with ambiguous and frustrating situations where they are unable to communicate as effectively as they would like;
- 2) Planning for interpreting needs rather than relying on family members and/or friends of clients/patients who happen to speak the language;
- 3) Developing programs to identify and train interpreters; and
- 4) Offering Spanish language courses for providers.

Example

The New York City Health and Hospitals Corporation has a mental health interpreter training program. They first identify bilingual staff members, and screen them to assess their potential ability for interpreting in addition to their

language skills; the staff member then participates in an extensive training program to learn simultaneous interpreting.

Simultaneous interpreting is like the interpreting you see at the United Nations. The interpreter becomes the conduit for information for the provider and the patient without being a third party in the interaction. This approach has the advantages of giving the provider control over the interview as well as the security of knowing that information is being delivered by a trained interpreter. (COSSMHO, *Across Cultures*, 1988 [2].)

Barrier 2: Misunderstandings Arising From Differences in Cultural Expectations, Communication Styles, and Values

Verbal communication among Hispanics tends to be guided by the cultural values of *respeto* and *personalismo* (respect and personalism). As a result, when interacting with a health provider, many Hispanic patients tend to avoid confrontation and conflict by not disagreeing, not expressing doubts about the treatment plan, and, often, by not asking questions. [2].

The provider's expectation may be that if someone has a question they will ask it, and they will assume if nothing is being said that the patient is in agreement with what is being suggested. Understanding and respecting differences in values and communication styles is a first step to alleviating miscommunication. However, this often requires a shift in the perception of the individual provider from "I am right, this is the way we do it" to "there may be different ways of handling and dealing with this situation."

A colleague and friend once said that understanding another culture is the work of a lifetime—actually, perhaps two. One lifetime to understand our own culture and its limitations, and the other to appreciate from that perspective both the excellencies and the shortcomings of another culture in a non-judgmental yet critical manner. He reflects my assumption that because we have failed to grasp the goodness and the limitations of the cultures we live in, we reduce other cultures to a mirror image of our own (F. Ponce, Feb., 1989, speech).

I would add that when that mirror doesn't show us back what we expect, we are disappointed, often angry, and criticize others. It is much harder to look behind that mirror and see an individual different from ourselves standing there.

**Barrier 3: Hispanics' Mistrust of the Health Care System
Born Of Negative Experiences**

Trust is a critical ingredient in building a relationship—often the most important. As we all know, it is usually not given freely; rather, it is developed and nurtured over time. In Hispanic culture, the value of *personalismo* stresses trust and the importance of personal, rather than impersonal or institutional, relationships.

Personalismo stipulates that the relationship of the patient is with the individual provider, not with the institution [3].

This attachment has significant implications for the provision of services. Rotating staff so that Hispanic patients are constantly seeing new people is not an effective way to encourage their participation and maintain them as patients. Bilingual and bicultural staff who have relationships and rapport with the Hispanic community need to be nurtured as valuable employees. They are often the link. If they go, the patients may go with them.

Barrier 4: High Medical Costs

- One in four Hispanics live in poverty; 27.1% of Hispanics lack health insurance, compared to 10.1% of blacks and 7.7% of non-Hispanic whites [4];
- 21.7% of Hispanic females are employed in service occupations, compared to 9.0% of non-Hispanic females [5]. Workers in service occupations often do not have health insurance.

Barrier 5: Cultural and Class Stereotyping

A *stereotype* is “a standardized mental picture that is held in common by members of a group and that represents an oversimplified opinion.” Some of the stereotypes that exist about Hispanics are:

1. Hispanics are new arrivals.

Fact: Less than 28% of Hispanics are foreign-born. The majority of U.S. Hispanics are at least second-generation Americans. Many Hispanics in the southwest cannot be called “arrival” because they never even crossed a border. They have lived on the same land for generations and generations [6].

2. Hispanics all speak different languages.

Fact: Most speak Spanish. In all languages there exist “regionalisms” and colloquialisms. Ability levels for reading and writing English and Spanish vary among Hispanics.

3. *Hispanics are only a small part of the population.*

Fact: As of 1988, there were about 19 million Hispanics on the mainland, and 3 million in Puerto Rico (U.S. Bureau of the Census, 1988 [5]).

Hispanics/Latinos are a people of difference. They are heterogeneous. Hispanic is actually the U.S. Census term to designate individuals of Spanish origin or descent. Hispanics are Mexican, Mexican-American, Puerto Rican, Cuban, Cuban-American, Spanish, Central or South American. Hispanics are a mosaic of culture, race, and ethnicity. Some are white, some are black. Some have been here for generations, some arrived as recently as yesterday. Some are citizens, some are undocumented. Some speak only English, others only Spanish, many both.

They are a heterogeneous population with a shared language and cultural values. They are a young population, with a median age of 25, as compared to 32 among non-Hispanic whites (U.S. Bureau of the Census, 1985).

Barrier 6: Institutional Policies That Display Insensitivity Toward Hispanics

Institutional policies may not consider important Hispanic values, such as hospital policies that limit visitors to only two people [8]. Hispanics are very family-oriented and want to have the family around, particularly during times of stress. Policies may simply not reflect the realities of the lives of those they are intended to serve.

Most of these barriers are not insurmountable, yet they require careful attention to the question that we first started out with: Who needs care, and what implications does that have for how it is designed, developed, and delivered?

There are two other areas that are relevant to genetic screening and I would like to highlight them quickly. These are the high prevalence of diabetes among Hispanics, particularly gestational diabetes, and the issue of late entry into prenatal care.

The prevalence of diabetes is two to three times greater among Mexican-Americans and Puerto Ricans than among non-Hispanic whites. One of the most disturbing findings of the Hispanic Health and Nutrition Examination Survey, conducted by the National Center for Health Statistics, was that of those individuals with diabetes, 40% of Mexican-Americans, 45% of Puerto

Ricans and 63% of Cuban-Americans are unaware that they even have diabetes [9]. We have a lot of education to do.

Hispanic women are three times more likely than non-Hispanic white women to begin prenatal care in the third trimester or get no prenatal care at all. Except for Cubans, those who did receive prenatal care made fewer visits. Only about 60% of Hispanics (except Cubans) and non-Hispanic blacks initiate prenatal care in the first trimester of pregnancy, compared to about 80% of non-Hispanic whites [10]. This creates serious problems for the screenings normally done during this period.

This nation spends billions of dollars on health care, yet Hispanics receive only a fraction. Hispanics are often denied financial, cultural, and professional access to the health care system. Underserved populations face greater barriers accessing basic preventive health care and genetic services. These barriers are both financial and non-financial, and a comprehensive strategy is necessary to address them.

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UNEQUAL OPPORTUNITY

PEGGY SEENEY COOPER, M.S.

Unequal opportunity and complex issues create ethnocultural barriers that limit access to and use of medical care and genetic services. According to the Baltimore Evening Sun newspaper, there is a health care crisis in the black community that mirrors a national problem, affecting blacks and other minorities disproportionately.

The Journal of the American Medical Association reveals that a wall of social and economic barriers prevents many blacks from receiving the same medical care as whites. Statistics reveal that disproportionate numbers of American blacks live at or near the poverty level in situations where poor nutrition, high stress, unhealthy habits, and limited access to medical care tip the balance where genetic susceptibilities play a significant role.

Poverty is one ethnocultural barrier that contributes to below-standard medical care. Transportation to doctor's offices costs money. There is a lack of black doctors in lower-income communities which could be a source of referrals to genetic services. Many doctors do not accept medical assistance patients. Many families may not seek access to medical services because they are more concerned with day-to-day survival and putting food on the table. Homeless families have reached crisis levels. These communities are plagued with high crime and substance abuse. Teenage pregnancy is at record high levels.

Lack of medical insurance is a reality for the marginally employed: contractual workers, temporary workers, service and day workers, minimum wage earners, and migrant workers.

Insensitive or biased care-givers make it difficult to deliver services to a community that harbors these perceptions, as well as feeling that they will be abused or used as guinea pigs.

According to Paula Giddings, author of *When and Where I Enter*, racial oppression maintains a heavy heel on the black family. Despite the growth of the black middle class in the last two decades, the average income for black families with children is 55% that of comparable white families. Even among black families in which both husband and wife work, their median income is about 83% that of whites, according to the 1980 census.

Insufficient education is a major barrier to reaching the underserved population. The *Baltimore Sun*, in a report from the director of the city's public library system, reveals that more than 200,000 adult Baltimoreans are classified as functionally illiterate.

The Mott Foundation Survey in 1983 found that 71% of the mothers who had their first child at age 14 or younger dropped out of school, as did 50% of the mothers ages 14–17 and 33% of the mothers ages 18–19. The high school drop-out rate among teenage fathers, is similarly high. These young men are 40% more likely to drop out of school than their peers.

According to the 1987 *Federal Register*, more than 573,000 babies are born to teenage mothers each year, and half of these young women will not complete high school. Moreover, teenage pregnancy is often associated with long-term poverty, health defects, and other types of problems.

The majority of young people feel that they need access to meaningful social roles within their families, schools, and communities to give them a sense of competence, make them feel that they are valued members of society, and enable them to look forward to productive, responsible, and rewarding adulthood. A priority should be to promote and stimulate the development or expansion of community-based efforts designed to involve youth as active partners in identifying solutions to these problems.

Efforts to improve literacy rates, reduce high school drop-out rates, and/or enable pregnant or parenting teenagers to remain in or to return to school are to be encouraged. Because language and culture are so interrelated, modules that foster the use of English as a second language will enhance community-based efforts, as well as addressing the following topics: cultural mores, food preferences, child rearing practices, health and mental health attitudes, rules of expected conduct in that culture, and the roles of parents and elders within the family unit.

In 1986, the Baltimore, Maryland Alumnae Chapter of Delta Sigma Theta Sorority, Inc., received a grant from Associated Black Charities for the purpose of creating a teen pregnancy prevention and teen parenting program. Following the thesis that teen pregnancy is caused by a myriad of circumstances, we focused on some of the prominent causes, as follows:

- 1) Lack of education concerning teen sexuality and health;
- 2) Unstructured and unsupervised time after school;

- 3) Poor self-esteem and lack of motivation; and
- 4) Lack of recreational outlets.

A comprehensive program has been developed to deliver services to the lower Park Heights Community including an infant care center, a day care center, and a family support program and center. These services are currently located in a renovated school building purchased by the sorority from the city of Baltimore. Adjacent to this building is another renovated facility to provide shelter for homeless families for up to one year.

Outreach efforts include personal contacts with school administrators, nurses, counselors, students, churches, community service groups and organizations located in the area.

Reaching the underserved population through support personnel is recommended for the development of new services. Peer group counseling through trained personnel appears needed at neighborhood centers or designated locations within the community. Information should be made available and understandable to the population served, either in simple laymen's language or pictures, or the native language of the ethnic group, such as Spanish. Groups to be served may be identified in the following areas: learning impaired, emotionally impaired, physically impaired, and developmentally impaired.

Services to be offered have been identified as: physician referral and medical management (medications, equipment, physical therapy); health and nutrition: family, education, and social needs assessment.

Since many issues related to the provision of genetic services to underserved groups remain unresolved and services in many communities are inadequate, the Delta Family Support Center can serve both as a resource and a model to begin to break down the barriers to quality health care.

WORKSHOP

B. NEEDS ASSESSMENT: IDENTIFYING THE UNDERSERVED

ISSUES OF DEFINITION IN NEEDS ASSESSMENTS

DANIEL L. BRANT, M.S.W.

As the director of a genetic services program in the Pennsylvania Department of Health, I have been involved in a series of initiatives that have been directed at the collection of uniform genetic services data for a number of years, first in Pennsylvania, then in the Mid-Atlantic Region, and now the country. I have felt for some time though that my program planning would benefit from more formal needs assessment than I have done to date.

Needs assessment will involve very different interests and issues for each of us, depending on where we work and what we do. In regard to genetic services, needs assessment can and has been used in evaluating the needs of different population groups, such as a specific racial or ethnic group, individuals with a specific genetic disorder, and low income citizens. It has been used to evaluate the extent to which clinical genetic services reach people in different geographic areas. It has been used to evaluate the recognition of specific rare genetic disorders by various health care providers.

Let's look for a moment at some of the terminology involved in needs assessment and the rationale for doing it.

What is a need?

Jack McKillip says that a need is a value judgment that some group has a problem that can be solved. A need therefore involves values, has a target population, and includes a judgment that a solution exists. Needs assessment is the process of evaluating the problems and solutions identified for the target population [1].

Why do a needs assessment?

A needs assessment can be used to assure that funding is targeted to the highest priorities. It will assist with decision making about program development and implementation. It can be used in the evaluation of an intervention; and it can support funding requests.

Our speakers are actively involved in needs assessment—having recognized problems and considered solutions. They will assist us to focus on the utilization of needs assessment in relation to a variety of interests and issues.

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MEASURING THE IMPACT OF GENETIC DISORDERS

GEORGE C. CUNNINGHAM, M.D., M.P.H.

The title of this conference, "National Symposium on Genetic Services for Underserved Populations," is in a way a succinct statement of the problem. The national emphasis points up the problem of state-to-state variations in both services and populations. By definition, underserved populations are not part of our current clientele. Therefore, enumerating and characterizing these populations becomes a difficult problem. The specific reference in the conference title to genetic services raises the question as to what extent the underutilization of genetic services represents a unique problem, rather than another example of the lack of access to health care to these populations in general.

There have been several attempts to measure the overall impact of genetic disorders. Starting first with the genetic contribution to in utero death and stillbirths, there have been several estimates. It is generally accepted that over 40% of such deaths in utero and 6% of stillbirths and neonatal deaths are genetic. Since at this stage most of the mortality is related to chromosomal problems, it is not surprising to see that this effect is dependent on the age of the mother.

The residual genetic defects in liveborn infants have been estimated by several authors, but the estimates continue to increase as our knowledge of genetic disorders expands.

One indirect measure of genetic defects in liveborn infants can be obtained by analyzing birth defect monitoring programs. These programs are currently enjoying some popularity, largely based on the public apprehension about environmental toxins. While they differ in their design and resources, they all suffer from delays in ascertainment, investigation, data entry, and analysis. However, specific information on conditions of genetic interest can be teased out of these registries. The states are incompletely covered by these birth defect registries. Also, due to non-comparability of results of states, we can only derive incomplete national data on the defects studied.

The importance of genetic disorders in terms of expenses generated during hospital care has been estimated by several studies. The percent of admissions due to genetic disorders varies from 30% to 40%.

There is a major defect in our information on the burden of genetic disorders in terms of the volume of outpatient ambulatory care required. Prenatal diagnosis is an increasingly important component of prenatal care, but there are no national and few statewide statistics on the numbers of amniocenteses, chorionic villus samplings, or carrier studies performed. There is no count of the number of karyotypes performed annually, although New York and California have laboratory-based reporting systems. A limited karyotype registry exists that attempts to accumulate clinical signs and symptoms associated with each karyotype reported. However, it does not provide incidence or service data.

Although many university and major private medical centers have established special clinics for genetics, usually in the pediatrics department, there are few institutions that can produce data on volume of services or characterize the clientele, variety of services rendered, or the diagnoses made. In addition, many genetic disorders are seen in clinics that are not classified as genetic, such as hematology, neurology, developmental, etc.

I have been discussing the limited data on genetic disease in the general population. We are concerned today with a special subgroup—the underserved.

With respect to genetic services, we have begun very primitive attempts to identify these underserved populations, mostly by inference. If we can accurately count and characterize the users of genetic services, we can determine who is not using the services, if we have good demographic data on the entire

population. Alternatively, we can estimate need by extrapolation from information collected in small sample populations, or incidence studies of single conditions.

I shall attempt to describe some current data bases, starting at the national level. The lead agency for genetics in the federal government is the Genetic Services Branch (GSB) of the Office of Maternal and Child Health. The GSB has been handicapped by lack of staff and funds, and by bureaucratic barriers that have precluded the GSB from taking on this data collection function directly.

The Council of Regional Networks for Genetic Services (CORN) is a federally funded effort to improve quantity, quality, and availability of cost-effective genetic services in the United States. CORN was developed in 1985 in response to the need for an organization both to coordinate activities among federally funded, regional clinical genetic networks, and to implement programs of national significance that emerged from regional initiatives. CORN serves to facilitate communication between networks and to ensure communication with other agencies involved with genetic services, and maintains a strong focus on the public health components of genetic services.

CORN meets twice a year and serves as a forum for the discussion of a wide spectrum of issues in genetics. Representatives from each of the ten regional genetic networks, the Alliance of Genetic Support Groups, and the sickle cell programs comprise CORN. From time to time, other persons may be included to achieve regional, professional, and "area of interest" balance. The operational activities of CORN are carried out by the standing committees that address the identified major areas of concern. At present, committees include: Newborn screening, data and evaluation, finance, quality assurance, education, communication/liaison, and sickle cell disease. Committee chairpersons are members of CORN; committee members are selected by each region to best serve that region's interest; committee members are to represent relevant technical expertise as well as consumer interests. Committees study, plan, recommend, and implement programs that become priorities of the council.

An essential part of the CORN effort regarding genetic resources is to identify the current level and scope of clinical genetic services on a state-by-state basis. This task has been assigned to the data and evaluation committee. This committee has identified the annual collection of a minimum data set (MDS) as a top priority. The purpose for this is to document the volume and types of services delivered, provider types, and demographic characteristics of the popula-

tion served in genetics. This information will be extremely useful in preparing reports for federal funding, in planning for future service delivery, and will contribute substantially toward fulfilling the CORN objectives. Information based on these data will provide comparable data for use in local planning. The data and evaluation committee recommended that CORN/MDS data collection be introduced for FY 1987 data.

Each region has identified reporting units, which are generally providers of genetic services that are funded in part by federal or state funds, or are licensed or otherwise known to the state. In our 1987 data collection, we identified 121 reporting units. Some of these covered multiple sites of operations so that they do not correlate to the number of genetic clinics participating.

The MDS consists of 12 reports, 6 relating to prenatal diagnostic services, 5 to other clinical genetic services, and 1 to reference laboratory services. Data collected included prenatal patients by age, race, urban residence, indication for service, total served, and summary of findings. Clinical service data were collected for all of these except indication for service. In addition, a separate questionnaire is mailed to all state newborn screening directors to collect extensive information about this major genetics effort.

Since these data were collected retrospectively, without prior knowledge by the reporting centers of the format or definitions, we have considered this a first effort. We were more concerned with establishing the process as groundwork for future efforts at uniform data collection than attempting detailed analysis of these admittedly incomplete, and at times inconsistent, data.

We were, however, encouraged by the degree to which we were successful in collecting national data for the first time. We can see the potential for a truly useful and acceptably accurate national database that can be used to answer many program evaluation and planning questions. We will shortly be sending out questionnaires with only minor changes for 1988 data and again in 1990 for the 1989 data.

If we are ever going to document who the underserved are, where they live, and how well programs designed to serve them are succeeding, we will have to build on this MDS as a base, working with the regional and state data coordinators to do special data collection and analysis. An example of this approach will be discussed by Dr. McCabe.

We welcome and encourage your support and participation in this effort.

NEEDS ASSESSMENT FOR GENETIC SERVICES IN TEXAS

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The Interagency Council for Genetic Services (IAC) in the state of Texas is charged by the Texas legislature with determining genetic service needs and developing plans to meet these needs. The information that follows represents a portion of the data collected by the IAC in order to fulfill its statutory obligations. We feel that, while the Texas model is somewhat unique, other states and regions may be able to select and adapt certain aspects of this model in developing their own needs assessment programs.

The Texas Genetics Network (TEXGENE) is unique within the Council of Regional Networks for Genetic Services (CORN) as the only state that is designated as a regional network completely unto itself. New York approaches this model, but also includes within the Genetics Network of the Empire State (GENES), Puerto Rico and the U.S. Virgin Islands. Therefore, within Texas, we have the opportunity to develop plans through TEXGENE that we can bring before the legislature for action. The IAC is the mechanism through which we accomplish this task.

The IAC was established on September 1, 1987, after being created by Senate Bill 257 (SB 257), passed by the 70th Texas legislature. It was initially convened on March 10, 1988, although all members had not been appointed at that time. The first full meeting of the IAC was held on April 22, 1988. SB 257 established the IAC for an initial period of two years pending "Sunset review;" i.e., the IAC would be discontinued if it did not show substantial progress in meeting its legislative mandate. The initial report to the Sunset Commission was due in September 1988.

The composition of the IAC includes one representative each from the Texas Department of Mental Health and Mental Retardation (TDMHMR), the Texas Department of Health (TDH), the Texas Department of Human Services (TDHS), University of Texas Health Science Centers (UTHSCs), groups contracting with TDH to provide genetic services, and two consumers or consumer representatives.

Review of the organizational structure of the IAC and its interaction with the Texas legislature and TEXTGENE shows that policy flows from the legislature to the IAC and from the IAC to TEXTGENE. In turn, TEXTGENE serves as an advisor to the IAC and the IAC serves as an advisor to the legislature. TEXTGENE includes genetic service providers, state agency representatives, consumers, and professionals who make up the TEXTGENE Advisory Committee and its subcommittees, which include Education, Data, Quality Assurance, and Genetic Services. TEXTGENE also includes the Genetics Coordinating Staff, which provides staff support to both TEXTGENE and the IAC. Since neither the IAC nor Textgene has fiscal authority, this is supplied by TDH through the Genetics Coordinating Staff.

The statutory duties of the IAC, defined by SB 257, are as follow:

- (1) Survey current resources for genetic services in the state;
- (2) Initiate a scientific evaluation of the current and future needs for services;
- (3) Develop a comparable data base among providers that will permit the evaluation of cost-effectiveness and the value of different genetic services and methods of service delivery;
- (4) Promote a common state-wide data base to study the epidemiology of genetic disease;
- (5) Assist in coordinating state-wide genetic services for all state residents;
- (6) Increase the flow of information among separate providers and appropriation authorities; and
- (7) Develop guidelines to monitor the provision of genetic services, including laboratory testing.

The purpose of this study was to assess the current resources available for genetic services and determine the current needs for these services. With this information in hand, we felt that we would be in a better position to evaluate future needs for genetic services so that we could develop a coordinated state-wide plan.

The first step in this process was to learn who was providing genetic services. We designed a mailing insert that was included in information sent out by many of the medical and dental societies within Texas. These included the

Texas Medical Association, the Texas Dental Association, and the subspecialty societies for Dermatology, Family Practice, Neurology, Obstetrics and Gynecology, Ophthalmology, Orthopedics, Pediatrics, Pediatric Surgery, and Plastic Surgery. We mailed out 8,200 inserts, and 477 responses were received. Of these, 187 (39%) were from individuals who stated that they provided primary care genetic services within their practice. In general, this included counseling within the office and referral for additional consultation or laboratory study as required. Of these 187 primary care providers, 61 (33%) were in the major metropolitan areas within Texas: Dallas, Fort Worth, Houston, and San Antonio. One hundred twenty-six (67%) were outside these largest metropolitan areas. One hundred twenty-nine (27%) of the respondents described themselves as providing consultative genetic services. Forty-seven (36%) of these genetic consultants were in the major metropolitan areas with 82 (64%) outside of these areas. In general, the distribution of primary and consultative genetic services followed the population distribution within the state.

In another study (described elsewhere in the proceedings of this Symposium under the title "Initial Study of Medical Costs Associated with Selected Genetic Disorders in Texas" (Workshop IIC),) we attempted to determine certain demographic information about individuals with 11 selected genetic conditions. Those 11 disorders included cleft palate, congenital heart defects, cystic fibrosis, Down syndrome, hemophilia, muscular dystrophy, neurofibromatosis, phenylketonuria (PKU), sickle cell disease, spina bifida, and thalassemia/Cooley anemia. Part of this study was a determination of the geographic distribution of Medicaid claimants with one or more of these disorders. Those areas with more than 500 Medicaid claimants for these 11 disorders included Dallas, Houston, San Antonio, and the McAllen-Edinburg area of the lower Rio Grande valley. In general, the distribution of Medicaid claimants for these disorders followed the population distribution of Texas, with a somewhat disproportionately large concentration of these claimants in the border area of south Texas, probably representing the lower per capita personal income in this region and increased Medicaid usage as compared to the rest of the state.

Next we examined Texas counties in an attempt to ascertain whether the claimants and the services were distributed similarly throughout the state. For this comparison, we looked at those counties with 25 or fewer claimants

and those with more than 25 claimants, and the availability of either primary care or consultative genetic services within these counties. We found that only 8 of the 254 counties in Texas with 25 or fewer claimants, had genetic services available. In general, where there were more than 25 claimants, services were either available in that county or in a neighboring county.

Finally, in a preliminary analysis of these data, we attempted to ascertain whether there were geographic barriers to Medicaid utilization for individuals with these 11 selected genetic disorders. In other words, we asked 1) how Medicaid dollars were being spent in the rural versus the metropolitan counties of Texas, and 2) was there a difference in Medicaid expenditures for these 11 disorders, based on the size of the metropolitan area. We based this analysis not on the dollars spent per claimant, but rather on the dollars spent per capita, in an attempt to evaluate how the money was distributed over the entire population. Recognizing that each individual is at a somewhat similar risk for genetic disease, we were asking, "What is that individual's access to Medicaid dollars for these 11 selected disorders?" We found that, across the state of Texas, with 16,685,000 individuals, Medicaid spent \$3.88 per person for these 11 disorders. The highest payments per capita in the population were in the smallest metropolitan areas, those with populations under 100,000; the amount paid was \$11.16 per capita. The lowest per capita payments were in the largest metropolitan statistical areas, those with populations greater than or equal to 1,000,000; in these areas the payments per capita were \$2.90. The non-metropolitan rural areas had payments of \$4.76 per capita and the areas with 100,000–250,000 and 250,000–1,000,000 people were \$4.38 and \$4.87 respectively. These payments were for a nine-month period from April through December of 1987.

SUMMARY

In summary, we found that the availability of genetic services for the Medicaid patients with the 11 selected disorders follow the general population distribution for Texas. In general, there is no major geographic factor limiting availability of services. We also found that the calculation of Medicaid dollars paid according to the size of the metropolitan area in which the patient resides indicates that there are fewer Medicaid dollars spent on

these 11 genetic disorders per person in the population in the larger metropolitan areas.

We conclude that preliminary review of these data indicate that the urban poor may have a greater need for medical services that deal with genetic disease.

STATISTICAL REPORTING OF GENETIC DISORDERS

PRISCILLA CICCARIELLO, B.A., M.L.S.

It is understood that statistical information is necessary to document prevalence of diseases. It is also evident that increasing competition for funds and health services has increased the imperative for the gathering of such statistics in order to estimate need and to distribute resources. One reads of on-going government-sponsored, epidemiological studies on cancer, AIDS, heart disease, etc., so it comes as a shock to find that there are few statistics being compiled for the over 5,000 rare and genetic disorders known today.

In 1976, the National Education Committee released the report, "The Killers and Cripples," which reported on medical services in the United States. In that report, genetic diseases were referred to as "the oldest, most widespread and probably the most burdensome of all human afflictions [1]." It was then estimated that there were 12 million Americans suffering from genetic disorders. Now, 14 years later, the National Commission on Orphan Disease has released the results of their two-year study, which estimates that closer to 20 million Americans suffer from approximately 5,000 rare and genetic diseases [2]. The National Commission on Orphan Diseases was established in August, 1985, and their report is the result of numerous public meetings, hearings, and surveys.

Among the concerns raised in the report was the need expressed by voluntary genetic organizations for a greater emphasis on the proper classification and the need for comprehensive statistical reporting of rare and genetic disorders. The reporting of genetic statistics was seen as a means to increase awareness of these disorders and to provide official recognition of the problems that they pose. Included in the report of the National Commission for Orphan

Diseases are the results of a survey of 800 voluntary health organizations which provide evidence of the devastating effect that genetic diseases have on individuals and their families. This impact is due largely to the ignorance of the medical community concerning genetic diseases, as well as inadequate health insurance and social services. The commission identifies as a major problem the lack of available information which could more accurately quantify these problems.

LACK OF STATISTICS ON GENETIC DISORDERS

When describing the features of a specific disease to someone who has never heard of it, the question asked is: "How many people have this disorder?" There was a time following the diagnosis of Marfan syndrome in my family that I believed we were the only ones affected, and this perception was reinforced by our doctors who would candidly remark that my husband and sons were the first patients with Marfan that they had seen outside of a textbook. A sense of alienation and dismay grew from this apparent uniqueness in my family and the lack of knowledge of the doctors. The personal impact of their attitude and the sense of alienation was devastating, compounding the already painful loss of a son in 1969 and my attempt to cope with medical and financial problems. It was only after the link-up with a support group—the National Marfan Foundation (NMF)—that years later my equilibrium and perspective were restored.

During my activities in the National Marfan Foundation as it grew into a full-fledged voluntary health organization, I, too, began to question just how many there *really* were in the U.S. with the Marfan syndrome. As a reference librarian and in my capacity of chair of the NMF, I attempted to track down these elusive figures.

I was appalled to find no statistics on the Marfan syndrome available from the National Center for Health Statistics, or the Centers for Disease Control, both government agencies within the Department of Health and Human Services. Nor were there any reports or studies issued under the *Morbidity and Mortality Weekly Reports* (a publication of the Centers for Disease Control) which carries in-depth statistical studies on many infectious diseases.

I then contacted the New York State Department of Health, where I learned that there were no statistics, because there is *no mandated reporting on either state or federal level for genetic diseases*.

PROBLEMS WITH CLASSIFICATION

Directed to the *World Health Classification of Diseases* (ICD), I reviewed the 23 major categories under which the world's diseases are grouped numerically and under which diseases are statistically reported. There were few single genetic diseases listed. Of those disorders listed that had multiple system involvement, most were found under a broader category, but not listed under the name of the specific disorder. I found many disorders grouped together under a single numerical assignment, such as the Marfan syndrome, which was listed under 759.8, a number that included 20 other unrelated disorders! (See chapter appendix, page 65.)

Further compounding the problem, the National Commission on Orphan Diseases reports that there are nearly 6,000 hospitals participating in the Medicare prospective payment system which use the Diagnosis Related Groups (DRG) classification for reimbursement purposes. The DRG system is a modification of the WHO ICD classification and breaks down the 23 categories into 470 groups, which again are structured by category, not single diseases [3]. These categorical assignments are also used in the "Listing of Impairments" for the Social Security Disability Administration establishing criteria for disability as well as providing the criteria to qualify for benefits from Medicare, the Developmental Disabilities Administration, and the Crippled Children's Services. The names of rare and genetic disorders are not included in the "Listing of Impairments" even though there is a category involving multiple systems which lists only five disorders: Hanson's Disease (10.02); Polyarthritis or periarteritis nodosa (10.03); Puli's (10.04); Scleroderma (10.05); and Obesity (10.10) [4].

CURRENT SCREENING PROGRAMS

There are fewer than 10 genetic disorders that have chromosomal markers which enable them to be identified in prenatal screening programs, or those disorders that produce by-products that result in diagnosis and can be screened in new birth screening programs now in place in many states (Table I-1). These screening programs—valuable though they are—by definition exclude the many thousands of genetic disorders that have no markers as yet, but that have late onset of identifiable complications. It is questionable if prenatal programs, as they now exist, would be capable of incorporating the large numbers of

genetic diseases that will become identifiable as research reveals chromosomal markers.

Unfortunately, the current dearth of statistical reporting perpetuates the lack of awareness and resultant problems posed by genetic disorders.

IMPACT OF GENETIC DISORDERS

Genetic disorders can be devastating because several members of a single family can be affected. One family can have several chronically ill children as well as a parent, all of whom experience alternating periods of critical and catastrophic illness. This places unbearable strain on the family emotionally and financially.

Table 1:
Diagnosible Conditions at Birth
Screened in the Newborn Screening Program

DISORDER	MCKUSICK NUMBER	INCIDENCE
1. Hyperthyroidism, familial	27500; 14565	?
2. Homocystinuria	23625, 23613, 23620	1:20,000 ?
3. Galactosemia	23040, 23035	?
4. Maple Syrup Disease (MSUD): Branched Chain Ketoaciduria	24860	1:125,000 1:300,000
5. Phenylketonuria (PKU)	26160	1:15,000
6. Sickle Cell Anemia	14190	1:1875 black population
7. Cystic Fibrosis (Mucoviscidosis)	21970, 25324	1:2000
8. Biotin-responsive Inborn error	21020, 21021, 25327	?

HEALTH INSURANCE

Compounding this, people with genetic conditions do not qualify for medical insurance because the condition is a pre-existing one. Many young children will *never* be able to get health insurance because of their diagnosis. The very conditions that are treatable and receptive to *preventive medical care* are not treated, due to the expense, and to lack of health insurance to cover the costs. Even if the patient had insurance *before* diagnosis, many necessary procedures and tests are refused coverage.

DIAGNOSIS

Few genetic conditions have chromosomal “markers,” making diagnosis of specific diseases difficult, often delaying identification of the disorder for several years. The National Commission report states that survey respondents complained that it took an average of six years for diagnosis resulting in exorbitant medical fees and delayed treatment [5]. It will take a greater emphasis on basic research to properly identify these disorders. Greater knowledge of genetic diseases will enable both affected persons to receive better medical care, and help establish more accurate reporting of incidence of the disorders.

COMPETITION FOR SERVICES AND FUNDS

There are now over 140 voluntary health organizations that are working to promote the concerns of their specific disorders, such as the lack of adequate medical care, health insurance, and sufficient social services. Many organizations fund and support molecular and clinical research on the cause and treatment of their disorder. Research has a very high priority because it is only by knowing the cause that there can be hope for adequate treatment and an eventual cure. Sadly the absence of statistical information on these conditions makes it difficult for the organizations to develop strategies or document funding proposals.

MEDICAL SCHOOL CURRICULUM AND CONTINUING EDUCATION

The National Commission on Orphan Diseases documents in its survey that research on rare and genetic disorders is not being adequately funded [6]. Current medical knowledge is slow in becoming available to the medical pro-

fession and indeed, human genetics courses are not included in the curriculum in many of the medical schools in the United States [7]. In many cases, the medical community has not kept pace with the new technological advances in medicine and how these new technologies can be used in diagnosing and treating genetic disorders.

SUMMARY OF THE PROBLEM

It is not just a question of mandating the reporting of genetic diagnosis and treatment on a state and federal level—although this is primary—but also a greater governmental commitment to fund research in order to increase the basic knowledge of these disorders. This commitment should grow out of the acknowledgement of the impact that genetic diseases pose not only on the estimated 20 million affected, but on society at large.

In summary then, in order to have qualified, comprehensive statistical reporting for genetic disorders we must overcome four major problems:

- 1) The lack of a perceived imperative by the governmental policymakers for the statistical collection of genetic disorders;
- 2) The lack of specificity in the World Health Organization (ICD) for rare and genetic disorders;
- 3) The lack of state and regional cooperation in statistical reporting of genetic disorders; and
- 4) The lack of simple diagnostic tools to provide accurate diagnosis.

STEPS TO BE TAKEN

Positive steps must be taken to improve the deplorable situation of people who suffer from genetic disorders which the lack of comprehensive statistical documentation serves to perpetuate:

- 1) Legislators must be made aware of the imperative for allocating funds for the reporting of genetic diseases. The medical community and voluntary health organizations must rally behind the report of the National Commission on Orphan Diseases to promote awareness of the medical and social needs of those affected with genetic diseases;
- 2) Pressure must be placed on the Centers for Disease Control and the National Center for Health Statistics to accept the responsibility for

development of statistical models that can be replicated for specific disorders and for generating comprehensive statistical reports on genetic disorders.

- 3) Greater research funds must be allocated by the National Institutes of Health both intra and extramurally for research on rare and genetic diseases to improve diagnosis and treatment, and to locate "markers" for these disorders which will ultimately improve the statistical reporting of genetic disorders.

The improved statistical reporting of genetic diseases will in turn provide further evidence of the great need for more equitable distribution of our country's resources for services and medical research.

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CHAPTER APPENDIX

INTERNATIONAL CLASSIFICATION OF DISEASES (I.C.D.-9) 9th EDITION

Marfan Syndrome Classification Assignment - 759.8

Syndromes Classified 759.8:

- 759.8 Alport's (hereditary hematuria - nephropathy deafness)
Bardet-Biedl (obesity, polydactyly, and mental retardation)
Beckwith (-Wiedemann)
Carpenter's syndrome
Cerebrothepatorenal syndrome
Cockayne's syndrome (microcephaly and dwarfism)
Cornelia de Lange (Amsterdam dwarf, mental retardation, brachycephaly)
Freeman-Sheldon (Whistling face)
Gorlin-Chandhry-Moss syndrome
Menkes'
Meyer-Schwickerath and Weyers (dysplasia oculadentodigitalis)
Mohr's
Papillon-Leage and Psaume (orodigitofacial dysostosis)
Rubinstein-Taybis (brachycephaly, short stature and mental retardation)
Rud's (mental deficiency, epilepsy, and infantilism)
Russell (-Silver) (congenital hemihypertrophy and short stature)
Taybi's (otopalatodigital)
VATER
Weill-Marchesani (brachymorphism and ectopia tentis)
Willi-Prader (hypogenital dystrophy with diabetic tendency)

WORKSHOP

C: ECONOMIC BARRIERS FROM THE PROVIDER PERSPECTIVE

ECONOMIC CONSIDERATIONS IN PROVIDING CLINICAL GENETIC SERVICES

REED E. PYERITZ, M.D., PH.D.

This symposium focuses appropriate concern on those consumers who are not receiving sufficient attention by the medical establishment in the United States. To no one's surprise, economic considerations have played a prominent role in creating today's intolerable situation and will be equally important in effecting change. From the consumer perspective, economic issues are well-articulated in this report. Less well-appreciated, however, are the ways in which the financial characteristics of the specialty of clinical genetics and the current system of delivering these services will influence comprehensive solutions. One of the workshops dealt with this area, and certain barriers to and strategies for removing them are summarized in the workshop recommendations (see page 257). This brief paper reviews some of the background information that prompted this workshop, and provides justification for its conclusions.

GENETIC SERVICES ARE DIVERSE

Genetic services constitute an impressive and growing number of functions, that are delivered in markedly different settings by professionals of diverse interests and training. All of these features render any general analysis of economic issues hazardous, if not impossible. But a few characteristics, shared in part with several other medical subspecialties, set clinical genetics apart from the medical mainstream, and deserve emphasis. These characteristics have been discussed in the literature [1-4], and I will focus on recent developments.

AN ARRAY OF PROFESSIONALS PROVIDE SERVICES

Genetic services are provided by a variety of professionals: genetic associates with Masters-level training in human genetics social workers, nurses, laboratory scientists, Ph.D. medical geneticists, physicians with special training

and certification in clinical genetics, and physicians without special training. Several and perhaps all of these individuals might be involved in any given case. Indeed, the "team approach" is highly valued in this field. With the exception of the physicians, however, it is uncommon for any of these "team members" to submit a bill for their *professional* services in providing a genetic service (charges for laboratory tests are a separate issue). Yet these non-physician professionals provide services that are not only essential, but also time-intensive [5,6]. Because total reimbursement for a genetic service is limited to what the physician can charge for his/her time (see discussion of CPT codes below), social workers, genetic counselors, and Ph.D. medical geneticists must be supported by other mechanisms. In a nutshell, according to traditions that have evolved in America over the past thirty years, the costs of providing most genetic services are considerably higher than potential reimbursement. Given that potential reimbursement is rarely achieved or even optimized [3], is it any wonder that institutions think twice before establishing or expanding genetic services?

GENETIC SERVICES ARE SPONSORED BY INSTITUTIONS WITH WIDELY VARYING ALLEGIANCES: PROVIDERS HAVE VARYING FINANCIAL INCENTIVES (FROM NONE TO VERY STRONG) TO DELIVER SERVICES

Coordination and delivery of genetic services occur primarily in four settings: state public health administrations; academic medical centers (both state-affiliated and private institutions); medical institutions that are not principally academic in focus (state-affiliated and private hospitals, health maintenance organizations [HMOs], and other large medical establishments); and physicians (from board-certified clinical geneticists to family practitioners) in small-group or solo practice. These settings differ widely in the genetic services offered, the demographics of the consumers served, the training and interest of the providers in genetics, and, especially important for this analysis, the financial dependence of the provider on payment for the services rendered.

To give but one example of the potential importance of the latter point, consider a physician in some of the settings. The county health officer has a mandate to promote the general health of the population, and must provide as broad a range of services as possible within the limitations of budget, policy, facilities, and available expertise; this person is salaried and derives no benefit other than professional satisfaction and advancement for expanding services.

The academic geneticist, on the other hand, usually attains rank and salary increases through research, and, to a much lesser extent, accomplishments in clinical service and teaching. Physicians on the faculties of state universities often have mandated positions with reasonably secure salaries. In contrast, most physician-geneticists in private universities are on "soft money," must constantly forage for salary support (usually through research grants), and derive little direct remuneration from patient fees.

Clinical geneticists in non-academic settings are usually either salaried to provide genetic services (because the institution views such services as necessary to their overall mission) or paid directly from patient fees. Clearly, the financial incentives to see patients may vary enormously among different physicians; less well recognized is that the incentives of a practitioner may diverge considerably from those of the institution that sets general policy, such as what services to offer and to whom to offer them. For example, a physician salaried by an HMO may wish to make genetic services readily available to the people under his or her care, whereas the administration encourages "judicious" referral to specialists and may even offer financial incentives to physician employees who keep patient expenses low.

Finally, small groups and individuals provide genetic services. The past few years have seen private, fee-for-service genetic centers develop, documenting that entrepreneurship exists even in this medical subspecialty. Most such centers focus on services with a relatively high profit margin, such as prenatal and DNA diagnosis. Depending on education, interest, and fear of legal liability, the non-geneticist physician may or may not deliver genetic services such as counseling, but rarely charges for the "genetic component" of the overall service.

Thus, with respect to physician-providers, there exists clear and sweeping diversity in personal economic incentive (and even disincentive) to deliver genetic services to any population, let alone a medically disenfranchised one.

GENETIC SERVICES PROVIDED BY CLINICAL GENETICISTS RARELY INVOLVE PROCEDURES

This issue is important in the current medical economic climate. So-called cognitive services (a perjurious term at best) such as constructing a family history, making diagnoses of obscure syndromes, managing hereditary disorders, conducting library research, and genetic counseling are especially time-

consuming, even when compared to the cognitive services of other medical specialists. Most importantly, there is wide agreement now that cognitive services are charged at considerably lower rates (for equivalent expertise, time commitment, and so forth) than are the professional components of procedures. The only procedures that are integral genetic services are amniocentesis and chorionic villus sampling, and these are performed by obstetricians. In this regard, laboratory services, such as cytogenetics and biochemical genetics, are not considered procedures, and are often not performed or billed by clinical geneticists, who are nonetheless called upon to counsel the patient about the results.

Such inequities, most obvious to the public in terms of the average income of radiologists and surgeons as compared to that of pediatricians and internists, greatly hamper expansion of non-procedural services such as comprehensive care of people with rare disorders, whether supported by government or private funding. Stimulated largely by the Federal Health Care Financing Administration, models are being considered to bring charges and reimbursement for all medical services more into line with the actual labor involved. Chief among the possible modifications to the current system is the Resource-Based Relative Value Scale (RBRVS) [7,8], which will likely be evaluated in some pilot trial in the near future. Clinical genetics has not been one of the specialties selected for investigation. If it is not selected before an RBRVS system is begun, clinical geneticists will most likely be lumped with pediatricians; while this will result in modest improvement in payment for cognitive services, genetics will still lag behind other specialties in terms of income.

Admittedly, the discussion up to now has focused on gloomy, but utterly human, aspects of the wide discrepancy between the need for and the capabilities of genetic services. The medical and health care delivery system is so fragmented in the United States that wide diversity of incentives to provide care is not unexpected, and there is little reason to suspect that such discrepancies will disappear soon or that consumer advocates will have much influence. But other issues, perhaps more amenable to improvement, must also be addressed if the suggestions generated by this symposium are to be implemented.

GENETIC SERVICES NEED TO BE (RE)DEFINED

From a health policy viewpoint, genetics professionals must be explicit not only about what they do in terms of service, but also about what they call what they do. This latter issue concerning "naming" the services is looming di-

rectly ahead for the specialty. Doing nothing will surely eviscerate genetic services outside of fully subsidized programs. The specialty has two options that are not mutually exclusive. Genetic services must be defined for billing purposes in terms of current procedural terminology (CPT) codes. For example, the code "90020" for "Comprehensive New Patient Evaluation, Outpatient" is commonly used for a first visit to a genetic clinic. Part of optimizing clinical practice income involves choosing the proper CPT code(s) for the services the genetic team provides to the patient [4]. Unfortunately, except for a few codes designating specific genetic laboratory procedures, none subsume the number of personnel and time commitments necessary for cognitive genetic services. Hence, the second option is to generate new CPT codes specific for genetic services. While this sounds straightforward, it is virtually impossible at the present time. The codes are controlled by an American Medical Association-sponsored committee that admits to full membership only representatives of specialties recognized by the American Board of Medical Specialties; the American Board of Medical Genetics is not so recognized and is not likely to be in the near future. Thus, the prospects for effecting fundamental change in how third-party payers perceive genetic services are dim. But even effecting such change would be only half the battle.

THIRD-PARTY PAYERS MUST BE CONVINCED OF THE WORTH OF GENETIC SERVICES

Simply having a CPT code for a service is no guarantee that an insurer will pay. Each service is scrutinized by a third-party payer before it is accepted for routine reimbursement. For example, it would be pointless to generate a code for "genetic counseling" because insurers reimburse for virtually no forms of counseling.

In approaching third-party payers for special recognition of genetic services, data on medical necessity, community standards of practice, efficacy, and cost-benefit are essential. Few such data have been gathered on genetic evaluations, genetic counseling, pedigree analysis, and extended family studies. Laboratory and procedural services generally fare better in the acceptance process. Chorionic villus sampling and DNA diagnostic testing, both available widely only within the past five years, achieved reimbursement status promptly.

GENETIC COUNSELORS MUST BE LICENSED

In most states, only health professionals who are licensed can practice independently, let alone bill for their services. At present, no state licenses anyone to perform genetic counseling; at issue is the cadre of master's-level genetic associates trained to provide this service. Genetic counseling must now be billed under the name of the physician-geneticist, and, for reasons noted in the last section, cannot be called "counseling." However, few states are likely to perceive sufficient consumer or professional agitation to establish a licensing board. California and New York, each with dozens of genetic associates and strong state-sponsored genetic programs, would be the most propitious.

GENETIC SERVICES FOR UNDERSERVED POPULATIONS WILL REQUIRE SUBSIDIZATION

In the absence of substantial revision in reimbursement policies, private academic institutions, private sector medical care delivery systems such as HMOs, and for-profit genetic centers will not be able to financially support any extension of their expertise to the underserved; indeed, I fear stasis at best, and perhaps retrenchment, of current levels. Thus, the burden must fall on governments, both state and federal, to establish programs and to subsidize them heavily. This seems an appropriate allocation of funds, given that no matter how the term *underserved population* is defined, a strong public health component is implied. However, the staff to fulfill this role does not exist at this time. Physicians are not entering medical genetics in large enough numbers, and of those who are, most prefer laboratory investigation to clinical service. Current positions for genetic associates are unfilled, and it is especially important that people from a variety of ethnic groups, and possessed of special communication skills, be recruited to clinical genetics. But unless young people interested in careers in genetics see a strong and lasting commitment on the part of the public health sector, providing services to disenfranchised populations to any substantial degree is overly optimistic.

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WORKSHOP

D. CHANGES IN ACCESS FROM BIRTH TO ADULthood

A CLINIC MODEL

ROBERTA M. SICH, M.A., L.S.P.

My daughter, Stephanie, was born in the early hours of September 25, 1974. Neither my husband nor I had any hint during my pregnancy that Stephanie would be born with a major birth defect. As I was delivering her, there was a sudden flurry of activity in the delivery room and my obstetrician said that we had trouble. Within seconds, Stephanie was born. I was told that I had a daughter and that she was breathing fine. She had a major problem and a pediatrician was on his way to the hospital to examine her. Stephanie was whisked to an incubator before I had a chance to see her. When I saw my husband while I was still in the recovery room, he said that Stephanie had a serious birth defect and may or may not live. She would be transferred to Children's Hospital in Cincinnati as soon as possible in the morning. I could do nothing. "Give her the best possible treatment and don't let her suffer any pain. I'll have her baptized in the morning before she leaves."

Our minister visited me. Stephanie had been baptized. The staff I worked with at the hospital came by early to offer support and encouragement. My husband arrived and said that an ambulance was on the way. We talked about what needed to be done for our family while my husband went to Cincinnati with our baby. A nurse came in to announce that the ambulance had arrived, along with a physician from Children's Hospital. The doctor came to my room, introduced herself, and spoke about Stephanie's birth defect. Had I seen Stephanie yet? No. The doctor brought her to me. Stephanie was beautiful. I was encouraged to come and see her at Children's as soon as I was able. I could call any time to find out how she was doing. Someone would always be available to talk to us about Stephanie's progress. It would probably be the nurse who was caring for her. Come any time. Be with her as often as possible. Come any time.

The doctor took Stephanie with her. My husband left to follow them to Cincinnati. They were gone. I was left with reading material about what had happened to Stephanie. Stephanie's birth defect was serious. Complications could occur. She was in the most expert hands almost immediately upon birth. She would have the first of many surgeries before she had lived her first day! Hospital staff who knew me kept visiting. Flowers and cards arrived and there were more words of encouragement from friends and family. I left the hospital two days later, and went to Children's immediately.

Stephanie was in the neonatal intensive care unit. The staff was remarkable. Stephanie was doing fine. We were encouraged to touch her, bring toys, and hold her as soon as surgery permitted. Doctors and nurses spoke with us, explaining what had happened to Stephanie during her young life, and began giving us a clearer picture of what the future would be. We were fortunate—very fortunate—to have been placed in a clinic system of care for our daughter. The experience has not been without stress. Certainly the initial shock and the decisions that I left to my husband to make were not easy those first critical hours of Stephanie's life. However, the medical support system that was available to her made those medical decisions obvious. Give her the best treatment the system had to offer, no less.

We have been fortunate to remain in the clinic system for Stephanie's medical care. The model for children born with spina bifida is to have specialists in neurology, orthopedics, and urology attend to the major medical disabilities of this birth defect. The clinic we attend is staffed by a pediatrician and nurse who oversee the needs of each child. Following clinic visits, the specialists' summaries are compiled and sent to the family and to the family's local attending pediatrician or family practice specialist. Referrals are made by the clinic to specialties such as occupational, physical, or speech therapies; infant stimulation programs; special education services; and psychological services.

The system works. The child is not treated for specific medical needs in an isolated setting. Physicians have the opportunity to discuss the effects of their treatment in light of the whole child. Families are relieved of the stress of finding specialists, coordinating appointments, and travelling to each physician's office. The clinic system provides families with the opportunity to have one-stop medical service at a reasonable cost. Ease of obtaining service, lowered cost, and the philosophy of viewing the child as a whole are three major advantages to this system.

This clinic model is not unique to Cincinnati. There are similar clinics for children with spina bifida throughout the state of Ohio in each of the major cities. They are funded through the Ohio Department of Health, Bureau for Children with Medical Handicaps (BCMh). Standards of care have been established by BCMh as a means of providing for the basic medical needs of children with spina bifida in Ohio. Each clinic must meet the standards in order to be recognized as a provider and receive reimbursement.

CONTINUITY OF SERVICES

Clinics provide the medical attention for the child with a disability and, as much as possible, for other needs that the child may have, such as physical therapy. The child, however, is not the only member of the family affected by the birth defect. Every member of the family is affected. The stress, both psychological and financial, can be overwhelming. Other family members in need of specialized services may have neither the time nor the energy to find them. These unserved needs only intensify the stress experienced by the family, and can result in a breakdown of the flow of services to the child with the birth defect. In Ohio, BCMh has recognized the family's difficulties. To begin to meet these whole family needs, a special study has been established in Ohio.

The Bureau for Children with Medical Handicaps established standards for services to children with myelomeningocele in the mid 1970s. These standards included a requirement for provision of nursing and social work services to children and their families. Based on the results of this project, the Bureau anticipates development of a fee-for-service method to provide reimbursement for service coordination for BCMh-enrolled children with selected handicapping conditions.

Service coordination is defined as assuring, documenting, and evaluating continuity of care for children who are handicapped and their families throughout all phases of intervention, both within and across agencies. It includes ensuring that a child and his or her family receive needed additional services that are provided outside the scope of an individualized program. The objective of service coordination is improved continuity and comprehensiveness of services for the child and family (*ODH BCMh Grant Guidelines for Service Coordination for Children with Myelomeningocele*, 2/24/88)

THE PROFESSIONAL'S ROLE IN CONTINUITY OF CARE

Those professionals who initially work with the parents of a child born with a birth defect must lay a foundation for a positive attitude toward the newborn. Parents must view their infant first as a child, and second as a child with a birth defect. The family must be encouraged to accept support and should be assisted to seek that support as soon as it is recognized that there is a problem. No family should be deprived of these two initial messages: Child first, disability second; and help can and should be found. It is vital that the professionals who initially come in contact with these parents know how to access the resources available within their community and region. There should be no excuse for any member of the medical community not to know where to find supportive services for the infant and family.

Likewise, as the child and family grow together, professionals who come into contact with them must continue that initial attitude: Child first, disability second. Help is available. No one specialty working with individuals with disabilities should be working in a vacuum. No one specialty can meet the needs of the individual and family exclusively. Each specialty must recognize that an individual with a disability and his or her immediate family can have any number of unserved needs at any period in their lives. Changes in response to a specialist may be the result of a new problem, and the specialist must be prepared to assist the family or individual in seeking other resources to meet their needs.

The study currently being conducted by the Bureau for Children with Medical Handicaps in Ohio is addressing this broad issue. Service coordination is becoming a necessary reality for families of children born with birth defects. Medical technology is enabling children with more involved birth defects to survive. As a result, there are more needs to be met for the child, and more stress placed on the family.

THE PARENTS' ROLE IN CONTINUITY OF CARE

Parents must realize early on in the care of their infant with a birth defect that professionals should not be the ones to make decisions for them. Professionals cannot possibly know and understand the dynamics of each family. Parents and professionals must accept this fact. Major decisions concerning the child should be made as a team effort with the parents being accepted as a full member of that team. Parents have a unique role to play. They can and should bring to the team the overall picture of the child with the birth defect

and how that child fits into and affects the family. Team decisions will vary because of the unique input of one source—the child's parents. Parents must not be intimidated by other team members; they should participate actively in decisions made regarding their child with a birth defect. Because the parents are in the unique position of viewing that child in light of the entire family, needs not realized by professionals may be identified by them. Parents should seek out services for their entire family as they see the need for them. When other family members cannot cope with the stresses, the entire family suffers the consequences. No one family member should be denied their unique needs because of another. Compromises will be a necessary part of family life. Denial of needs will produce disaster.

Parents play a unique and vital role in the development of the child with a birth defect. They must be armed with a mind set for success by viewing the child first, the birth defect second. Richard Simmons once used the term "handicapable" to describe children with disabilities. Each is capable in his or her own way. Parents must build on the special things their child can do, not focus on the disability that cannot be changed. What can't be cured can be adapted. If a child can't walk, then bracing may be needed. If bracing is not the answer, then a wheelchair can fit the child's mobility needs. If a child can't learn in a traditional academic setting, then the setting should be adapted to meet his or her unique learning needs.

In learning to cope with a disability and adapt to a child's special needs, parents should seek a parent support system. Learning what other parents have experienced, learning about the laws and rights of children with disabilities, and being able to find someone with similar concerns are important for parents and child alike. Just as professionals should not work in a vacuum, neither should parents live in a vacuum. It is not healthy for child or parents to be isolated.

An article published by the National Information Center for Children and Youth with Handicaps (NICHCY) gives insight into the key role parents play in the early development of their child with a disability. The writer recommends that parents and professionals read "Early Intervention for Children—Birth Through Two Years," *NICHCY News Digest*, Number 10, 1988.

As a child grows, it is vitally important to teach decision-making skills. However difficult, parents must involve their child with a disability in making decisions at a young age. As much as possible, the child should be involved in medical care decisions. Parents must realize that it is the child's body that is be-

ing cared for—not the disability. Each child will have his or her own perception about his or her body, and parents must recognize this and develop positive experiences of control for the child. As the child enters school, parents should involve the child in the process of individual education planning. Individual education plans (IEPs) should not be developed for any student without respecting his or her opinions. Making decisions for a child with a developmental disability undermines any attempt at self control and serves to create a dependent adult. Parents must permit decision making, and allow the child to make mistakes and experience the consequences.

Parents are referred to a manual about self advocacy titled, *Roots and Wings: A Manual About Self Advocacy*, prepared for the Technical Assistance Parent Programs (TAPP), 1986. The manual can be obtained from PACER Center, 4826 Chicago Avenue South, Minneapolis, MN 55417-1055.

CONTINUITY OF SERVICES FOR GENETICS

Ohio residents can access genetic services through three programs developed by the state's Department of Health. The first means of access is a regional genetics center. These provide counselors to prospective parents, and parents of children with genetic birth defects. The centers, located in the major medical centers in all of Ohio's larger cities, gather genetic data that is collected by the Ohio Department of Health. Satellite clinics are being developed to provide genetic counseling in regions of the state where the service has not been previously available.

The second means of obtaining counseling is through the perinatal centers located throughout the state. Geneticists are part of the medical team caring for infants who are transferred to these centers. As part of their outreach programs, individuals interested in genetic counseling can be referred to a counselor.

A prevention network established by an Ohio Developmental Disabilities Planning Council grant provides a third means of accessing genetic services. The grant includes public health funding, and is focused on the rural health system and Ohio's education system. The prevention network provides a genetics curriculum to supplement that offered by Ohio's health education teachers.

BARRIERS TO THOSE REQUIRING GENETIC SERVICES AS CONSUMERS GROW OLDER

SERVICE COORDINATION

My own experience in working with parents in Ohio has shown that there is a lack of comprehensive service coordination—at best, it is fragmented. Service coordination often is limited to the period of time that a child is involved with a particular institution. Once the child is no longer receiving services from that institution, the coordination is left to the parents. Generally, the service is focused on the child only, with the family's needs left unserved. There is no one overseeing the whole family. Parents often seek help only when there is a crisis or a major change needed. They may not know what is available in their own community. The child may not be adequately prepared to successfully perform in a new setting because no one looked far enough ahead. It is a shock to anyone having to change schools, or go from living in the protection of a family home to independent living. The stress is greater and the chance for success is far less for the inadequately prepared young person with a developmental disability.

ADULT SERVICES

Coupled with possible lack of preparation to shift to new, more independent settings is the obvious absence of medical services for the adult with a developmental disability. As medical technology advances, children with more involved birth defects are living to adulthood. Birth defects do not vanish with the onset of adulthood, yet the medical support system does. A few clinics for adults with spina bifida have been established as the result of the strong urging of parents of young adults. The health care community must meet the needs of these adults. They have no time to wait. The medical community must develop research projects and data bases to assist with the establishment of medical services for them. The time to begin is now.

Along with the medical needs of the adult is the need for adequate medical insurance. It has been my experience in speaking with adults with spina bifida that the lack of adequate medical insurance affects their entire lifestyle. Opportunities for employment are often ignored because of the lack of medical coverage during the waiting period of an employer's insurance carrier or the re-

fusal of coverage because the developmental disability is classified as a pre-existing medical problem.

INFORMATION AND REFERRAL SERVICES

Adults with developmental disabilities may not know how to access available medical services within their state because their parents had never accessed the system. The adult may not know where to turn for help. As unique and popular as the clinic system is in Ohio for children with spina bifida, only a portion of Ohio's qualified families use the system. The medical community must advertise the unique programs that are available to the public. Medical service systems should actively seek and support information and referral sources that are provided to the public. In my own community, a special project entitled "First Call for Help" has been adopted by United Way to create an information and referral resource for our citizens. I have encouraged the project director to include information and referral sources for citizens who are handicapped. At the state level, there is an information and referral network being developed for individuals with disabilities and their families. The state project is called "Direction Services" and is being administered through the Ohio Coalition for the Education of Handicapped Children. Ideally, both systems should have access to each other's referral network.

All professionals working with individuals with disabilities need to receive training about information and referral systems. It has been my impression that professionals often work in a vacuum, not cognizant of information and referral systems beyond their unique professional network. Yet parents may express concerns about unserved needs to professionals who turn a deaf ear to them for lack of knowledge about information and referral systems. As services to the family and child with a developmental disability expand, access to the services must be made available to the general public, the family, and the professional: Information and referral systems must be held responsible for providing ongoing advertising campaigns to educate everyone about their services.

Finally, the professional must remember that he or she is assisting the family and the individual with the developmental disability. Decisions to accept or reject service will depend upon the unique needs of the individual and his or her family. Professionals must understand that any added requests to help the child with a disability at home means that the parents must find the time to work with the child. Parents may not be willing or able to sacrifice another time

commitment. Professionals often view this lack of time commitment as neglect or rejection of the child with a disability. Parents indeed may want to work with a child, but time does not permit the commitment within the unique requirements of that family. When professionals, parents, and individuals with disabilities view themselves as equal contributors to a team, the acceptance or refusal of a service can be understood. Each individual has goals that must be respected. Everyone in our society has access to the same 24 hours each day to accomplish their goals in life.

Theme **II** Barriers
to
Care

PLENARY ADDRESSES

AN OVERVIEW OF BARRIERS TO CARE

GEORGE C. CUNNINGHAM, M.D., M.P.H.

It is appropriate that this symposium should be addressing the issue of barriers to genetic services at a time when the problems of access and cost containment in the health care field are being vigorously debated at both the state and national levels. The United States leads the world in percentage of GNP (11%) spent on health care. In spite of this distinction, costs are escalating rapidly, problems of access are getting worse rather than better, and our health statistics are beginning to document poorer outcome with increasing frequency. Whether you read professional studies like the report of the National Leadership Commission on Health Care, or the daily newspaper, without exception the conclusions are the same—our health care system is sick and getting sicker. Polls show 89% of Americans believe the nation's health system needs fundamental change. This contrasts to 64% of the British and 42% of Canadians. This dismal performance reflects the failure to deal effectively with the poor state of education in this country, the problems associated with assimilation of large numbers of aliens, and, most importantly, the problems of financing. I would like to comment briefly on each of these.

First, financing of health care in the United States is a national disgrace, and a case study in inept planning and piecemeal solutions. Payment for health care in this country comes from a bewildering array of public programs, private insurance plans, or out-of-pocket sources.

Let me first dispense with private health insurance as a viable mechanism. In 1977, there were 25 million Americans without health insurance. This year, that number has increased to 37 million, an increase of over 40% in the past ten years. In 1979, insurance covered 52.5% of hospital bills; today, it covers less than 45%.

In the 1960s and early 1970s, unions were successful in obtaining employer paid insurance for their members. There is currently a lot of interest on the part of politicians to further transfer the financing of health care to employers by mandating health coverage. This is a complex and indirect way to raise the

money needed to finance health care, and an irresponsible attempt to avoid the unpleasant but absolutely necessary task of increasing taxes.

Attempting to pay for insurance coverage by forcing employers to pay for insurance is misguided, and will only compound our fragmented, inefficient, and inequitable system. This "solution" does not address:

- 1) Loss of coverage with loss of job;
- 2) Inability to obtain continuation under the Consolidated Omnibus Budget Reconciliation Act (COBRA) due to increased premium or a "pre-existing condition;"
- 3) Inability of small employers to afford truly comprehensive coverage;
- 4) Impediment to growth of small business and limits jobs;
- 5) Failure to cover unemployed;
- 6) Failure to cover part-time employees;
- 7) Failure to cover the self-employed;
- 8) The resultant wide variation of coverages, copayments, etc., irrespective of ability to pay;
- 9) The resultant demand by businesses to control medical decisions, limit choice of doctor, impose treatment restrictions, etc.;
- 10) Employers transferring costs to workers by limiting salary increases, or to customers by increasing prices. In 1982, 29% of employees contributed to premiums—today, it is over 46%;
- 11) Employers excluding family members and retirees from coverage; and
- 12) Instability, as employer can negotiate "give backs" of health benefits.

Traditionally, insurance was a mechanism to distribute the costs of care needed by a few across the many. However, the risk rating of applicants has eliminated many who will need care—diabetics, hypertensives, people with AIDS, those with family histories of breast cancer, etc., so that insurance is increasingly available only to the healthy. Blue Cross, for example, refuses to ensure 20% of the applicants for individual and family non-group policies, and limits coverage for another 20%. With increasingly accurate, predictive tests, such as DNA techniques, which can screen for populations at risk for a variety of chronic conditions, these percentages can only be expected to increase. Some have suggested, therefore, the creation of high-risk pools to cover these

"uninsurables." This patchwork solution would only contribute to inequity and escalation of costs. Nothing short of universal coverage will resolve this problem.

Furthermore, private insurance is not accountable for its nonuniform rates, administrative costs, scope of benefits, exclusions, and reimbursement policies. It has failed as a cost containment device in spite of increased competition, bureaucratic utilization controls, diagnosis related groups (DRGs), peer reviews, and preferred provider lists. Insurance rates have increased 15 to 25% while inflation in health care has increased only 8%, and utilization of services by 10%.

A recent financial analysis of health care financing predicted that by 1990, 47% of Americans will be enrolled in preferred provider organizations (PPOs), 22% in health maintenance organizations (HMOs), 20% in controlled fee-for-service, and only 10% in free choice fee-for-service insurance programs. We need, therefore, to look next at whether PPOs and HMOs promise a way out of our current quagmire.

PPOs were designed to limit costs by competition. Insurance companies negotiated coverage packages with hospitals that limited costs. After initial reductions, costs have increased dramatically, due to increased use, especially of outpatient services. Moreover, plans have had to increase both hospitals' and physicians' fees in order to have sufficient providers to attract subscribers. PPO plans compete with one another and with fee-for-service plans. The result in California is that plans that covered 7 to 9 million Californians increased costs 13.1% in 1986 and 15.2% in 1987. The experiment is not the answer.

HMOs were proposed as a way to provide cost-conscious quality care. HMOs also have become competitive. As a result, they are selectively enrolling the healthy. A survey of the 50 largest federally qualified health maintenance organizations revealed that 25% of applicants were denied membership. They are subject to misrepresentation, denial of benefits, and encouragement of dissatisfaction by those that use services.

Physicians who exceed HMO guidelines on utilization, or practice "expensive" care, are discharged. Mortality rates were found to be higher in highly competitive HMO areas.

Consider next the publicly financed sector. The two major programs are Medicaid for the young and Medicare for the aged. There are few proponents for

expansion of these programs. After their introduction in 1964 and initial growth, they have been systematically constrained.

Medicaid reached its high point in the 1970s when 65% of persons below poverty level were covered. Now coverage has decreased to 38%, and in some states is less than 20%. Over 800,000 women and children have been forced off the rolls as eligibility has been tightened. In addition, federal matching has been lowered. The net effect of these fiscal constraints is to transfer costs to providers as so-called uncompensated care. This has reduced access, as doctors and hospitals opt out of participation in these programs. The number of Medicaid providers, for example, has declined. Last year, California recorded a 17.4% increase in the number of physicians, from 59,053 to 69,303, while Medical physicians actually decreased from 39,193 to 31,610.

Medicare has failed to provide for those over 65 years of age. Thanks to decreases in covered services, increased deductibles, and copayments, the elderly have higher out-of-pocket expenses today than in 1960 when Medicare began.

In terms of financing health care, nothing short of a radical and fundamental restructuring will stop the drift toward unnecessarily expensive health care for some and inadequate care for many. The recent proposal by the Working Group on Program Design of the Physicians for National Health Program, published in the January 12, 1989, issue of the *New England Journal of Medicine*, should serve as a blueprint for discussion and development of national legislation. We, as genetic service providers, can contribute special insight and expertise on the inclusion of genetic services.

Until there is a resolution of the major fiscal problems on a national level, what financial techniques can be employed in the interim? The mechanism we have found to at least partially meet our needs in California is state-administered programs supported by user fees. This provides comprehensive, high quality prenatal and newborn screening at a very reasonable price to the individual. It is essential that the fees be calculated on the basis of the full cost of services and be deposited in a special fund whose use is restricted to genetic screening. This solution is not applicable to tests like amniocentesis, where large numbers of high-risk individuals, but not the whole population, need relatively expensive testing services.

Another approach is mandatory coverage by public and private third-party payers. State laws mandating specific coverages increased from 30 laws in 1970 to over 700 laws in 1988. This has contributed to the increase in self-insurance by employers, since such self-insured plans are usually exempt from mandated coverages. Mandated coverage has been used to cover prenatal diagnosis, genetic screening, etc., but obviously has limitations, such as increased premiums, or, as more and more services are mandated, refusal to sell insurance in the state.

The second major barrier to genetic services is the general ignorance of the U.S. population. This workshop is focusing on part of this problem when we refer to language barriers, but this is by no means the whole of the problem. Language is the basic mode of human communication. Inability to explain, to question and answer, to gradually achieve understanding by dialogue, is a major handicap to obtaining health care in a face-to-face encounter. The magnitude of the problem can be appreciated by one statistic. The Los Angeles school district now has 160,000 non-English speaking students who speak over 80 different languages. The communication problem is increased with monologues on audio or audiovisual tapes. Progress beyond verbal communication to being able to read in *any* language is a step that proves to be a greater communication barrier. Some estimate that by the year 2000, only one-third of the U.S. population will be literate in English.

The classic response to the language problem is the use of interpreters and translations. In the field of genetics, this is not a simple process. The concepts of basic inheritance; the details of limits, risk, and benefits of the complex techniques employed; probabilities; and statistical concepts like odds, ratios, informativeness, etc., are difficult to explain and not well understood even by English-speaking college graduates. After numerous attempts to lower the reading level of our patient information booklet for maternal serum alpha-fetoprotein screening, we could not reduce the reading level below 13th grade without leaving out some concept essential for informed consent. The Business Council for Effective Literacy reported that one in eight employees can only read at third grade level, and one in five cannot read at sixth grade level. Many recent surveys of the general knowledge of graduates of our schools demonstrate an abysmally low reading level, and a poor knowledge and respect for science. Only a minority of Americans can correctly locate the liver, or know

what body temperature is normal. In this environment, the Hispanic immigrant, the Hmong refugee, and the native-born field worker may all be unreachable.

Because of our need to communicate on all levels of society, we need to bind ourselves together by a commitment to fluency in spoken and written English for all our citizens. Major resources in the schools, in business, and in government need to be directed at all ages and ethnic groups toward this objective. The reverse process, promoting second languages or ethnic professionals, will only perpetuate the problems of communication and inequity of resource availability. We should produce an English version of all translated or foreign language materials on the same copy, as a matter of policy.

Finally, we come to cultural barriers. There is a strange paradox in humanity's attitude toward cultural differences. There is a simultaneous desire to fit in and adapt to the majority modern culture, while at the same time there is an emotional need to retain the ancient culture of our ancestors, without regard to the rational usefulness and value of each of their elements. History shows that, for better or worse, the culture of the dominant social, political, and economic groups generally prevails. However, no single set of cultural beliefs and practices has been so undeniably successful as to distinguish it from all others. Native Americans, Asians, Pacific Islanders, Aleuts, Hispanics, Armenians, Basques, Arabs, and Amish all have some beliefs in common and all have contributed unique insights of value. The attitudes toward various medical interventions; diet; and relationship to the healer and with the family and community are important determinants of both whether care is sought and whether medical advice is followed. We need to be aware of and respond to such cultural differences as exist in this country. At this point in our history, we still need special culturally sensitive clinics and services to provide a transition from these cultures to be able to provide the best that western medicine can offer. Western medicine needs to include effective practices from other cultures.

However, our ultimate goal should be to offer effective health services that improve the quality of life and that are universally available and acceptable. We all benefit and enjoy the differences between cultures in art, music, dress, and diet, but there can be only one science. Karyotypes are not tempered by cultural beliefs or practices. Coining or chewing peyote will not save lives when red cells are needed.

Genetic services, by their nature, are highly technical, complex, and require specialized equipment and a multidisciplinary team of experts. Therefore, they are available only in major metropolitan areas and medical centers. Many sparsely populated areas lack the resources to develop and support such specialized tertiary services.

In response to this problem, the federal government has used its national mandate to cross state lines and promote the development of multistate genetic service regions. Large states like California have developed service regions within states, which combine rural and urban areas to provide an accessible source of service.

Another solution is the use of satellites. These are genetic clinics that are held periodically, weekly, monthly, quarterly, staffed by a combination of local and metropolitan medical center staff. To be economically viable, such satellites need to be well planned, and have expert local coordination and acceptance.

A MODEL PERINATAL GENETICS PROGRAM

ILANA MITTMAN, M.S.

In the United States, perinatal genetic counseling interventions are considered the standard of care, with the number of individuals seeking such services steadily increasing. It is evident, however, that accessibility to such services varies greatly among different populations. This is due to the rather complex nature of the discipline of medical genetics, its relative newness, the high cost of procedures, and the limited availability of services. More likely to encounter barriers for care are low income, undereducated, and immigrant minority populations. The following is a description of a model program, established to tailor sophisticated genetic counseling interventions to the special needs of an underserved population.

The Perinatal System at San Francisco General Hospital (SFGH) is a 13-site, comprehensive, antenatal care system, serving a low income, uninsured/underinsured population in the city and county of San Francisco. The system serves 2,400 patients, with 2,100 deliveries annually, amounting to one-fifth of all de-

liveries in the county. Services available at the SFGH perinatal center include routine, high-risk, teen, and nurse midwifery obstetric care. Because of economic as well as linguistic and cultural factors, SFGH serves the largest immigrant population in the city and county of San Francisco. Of patients receiving care at SFGH, the largest group (44%) is Latino, mainly from Central and South America. Another 17% of the population is from mainland China and Hong Kong, with an anticipated increase in immigration when Hong Kong returns to Chinese control. Other recent arrivals include Southeast Asian refugees, Filipinos, Arabs, and Western Europeans. Almost all of the Asian patients and half of the Latinos are monolingual. As a whole, only 25% of patients claim English as their primary language and 60% are monolingual in a language other than English. The socioeconomic profile of the patients served by the system is typical of recent immigrants. The majority reside in poorer areas marked by high crime and drug dealing, such as residential hotels and city housing projects. A significant proportion of patients and their partners are unemployed and most of the remaining hold nonprofessional minimum wage jobs, without health care benefits.

The average level of education of these patients is estimated to be below the seventh grade level. As many as 30% of patients do not have a supportive partner, and 67% require social work intervention. As many as one-fifth of prenatal patients are in their teens, and 7% are over 35 years old. SFGH patients demonstrate poor prenatal care practices, with 40% of patients presenting for care after 20 weeks of pregnancy, and 10%-15% who do not receive any prenatal care at all. There is a high incidence of gestational diabetes compounded by poor nutritional habits, and 16% of patients are documented as substance abusers.

The health insurance status of the patient population is also typical of an indigent population. Only 3% of patients have private insurance, 27% are Medi-Cal recipients, 51% enroll in the SFGH low-cost maternity benefit package, and the remaining patients are Medi-Cal eligible. (Due to recent changes in Medi-Cal regulations, up to 70% of patients may be Medi-Cal eligible by June of 1989. The SFGH low-cost package will then be restricted to individuals who are ineligible for Medi-Cal.)

A number of factors contribute to the need for genetic counseling services in the SFGH patient population. Substance abuse, predominantly cocaine and alco-

hol, is identified by history and toxicology screens in 16% of the patients. Significantly high or low maternal serum alpha-fetoprotein (MSAFP) levels are noted in 10% of the patients, a figure that is twice as high as that seen in other institutions. Clinically significant hemoglobin variants are seen in 10% of the patients. Another 7% of women are 35 years of age or older, and 1% have pre-gestational diabetes. Currently, 1% of the prenatal population have a positive HIV-antibody screen. Other indications for services include teratogen exposure, positive family history for genetic conditions, consanguinity, and previous offspring with congenital anomalies.

Prior to the initiation of the SFGH Perinatal Genetics program, on-site genetic counseling and testing services were only available for hemoglobin disorders through the Northern California Comprehensive Sickle Cell Center (NCCSCC). For other indications, patients were referred to a tertiary regional genetic center at the University of California Medical Center, providing both prenatal diagnosis and medical genetic evaluation. Despite the availability of services, the SFGH population did not take advantage of the genetic counseling and testing services when they were offered off-site. This was shown by the fact that of 150 patients identified with advanced maternal age in pregnancy, only 14 (8%) had prenatal diagnosis performed. This acceptance rate is significantly lower than the 50–60% rate for acceptance of prenatal diagnosis for the same indication reported across the country. In contrast, of prenatal patients identified as having an abnormal hemoglobin variant, 86% had genetic counseling and 70% had their partner tested. The differences in the utilization rate of the above genetic interventions were due to the limited accessibility of the SFGH patient population to the regional genetic interventions at UCSF.

Several barriers to accessing care were identified and include:

- *Unfamiliarity with the institution.* Since many of the patients are new immigrants, there is a strong preference to stick with the familiar. Patients identify with the SFGH system as their primary health care institution and feel uncomfortable with outside referrals.
- *Linguistic barriers.* As translation services were limited at UCSF, patients were required to bring their own translators to the counseling session. Some of them had to rely on their American-born children

while others used a friend or an acquaintance, for a rather delicate translation of information. Others simply were not able to comply with the requirement. In addition, patients were required to make their own appointments and were unable to do so because of linguistic barriers.

- *Ethnocultural barriers.* Many patients are unfamiliar with Western medical practices and therefore do not understand the reason for referral or what is anticipated at the visit. In addition, different cultural beliefs about illness, child bearing, and birth defects were not always recognized by the providers to allow for culturally sensitive and supportive counseling. As genetic counseling is usually done the same day as the procedure at UCSF, patients feared the unknown and were intimidated. Of patients who did follow up with their UCSF appointments, many reported getting lost or feeling out of place because of obvious cultural and socioeconomic differences.
- *Educational barriers.* Given the low educational background of this patient population and their lack of sophistication in medical terminology, a brief slide show and counseling session, provided on the same day as the test, are not sufficient to promote understanding of the procedure among these patients. In addition, take home educational materials about the test were not available at appropriate literacy levels. This proved to be a problem, as many of the patients presented to counseling without their partner and needed to educate them about the procedure before they could consent to it.
- *Economic barriers.* Since as many as 84% of patients lack a third-party reimbursement source in their second trimester, funding for genetic interventions was another significant barrier. Although funding was available for amniocentesis performed for advanced maternal age through the California Regional Center for Developmental Disabilities, funding was not available for patients needing medical genetic evaluation and other specialty services. In addition, since as many as 20% of the SFGH patients are undocumented aliens, these persons do not qualify for state funding and are unable to use services.

Realizing the need for culturally and linguistically appropriate genetic interventions in the SFGH population, the Department of Ob/Gyn and Reproductive Sciences at UCSF/SFGH and the local Sickle Cell Center, applied for federal funding to establish an on-site genetic counseling and testing program. A three-year grant was awarded from the Maternal and Child Health Division through the special projects of regional and national significance (SPRANS) mechanism. The grant was awarded to develop a model system for provision of genetic counseling services to an underserved population. A perinatal genetics program was established at SFGH under the leadership and direction of the UCSF Reproductive Genetics Unit. The program serves perinatal patients at risk for offspring with birth defects, parents of newborns with congenital anomalies, and other individuals in their child-bearing years seeking genetic consultation. Two full-time genetic counselors and two part-time bilingual/bicultural Chinese and Spanish translators were hired. Space was provided by the Sickle Cell Center and a counseling program providing prenatal diagnosis counseling, general genetic counseling, and hemoglobinopathy counseling was established on site at SFGH.

The program's translators have the following backgrounds: One is a nurse midwife from Hong Kong who has been in the United States for two years, and was selected for her abilities in Mandarin/Cantonese translation; and the Spanish translator is a woman of Nicaraguan descent, who although raised in the United States, was brought up maintaining the cultural practices of her country of origin. The Spanish translator previously worked in the SFGH Ob/Gyn department on the secretarial staff but desired a health education role. Both translators received training in the basic concepts of human genetics, genetic counseling, and prenatal diagnosis from the program's genetic counselors. In turn, they educated the program's counselors in cultural beliefs pertinent to service delivery. In addition, both translators were trained and certified by the State of California Genetic Disease Branch as hemoglobinopathy educators/counselors, and provide independent counseling in this area. In other counseling situations, the translators work together with the program's counselors in providing counseling services. For languages other than Mandarin/Cantonese and Spanish, the hospital's translation services are used.

Criteria for referral were established and multiple in-service sessions were given to the different hospital providers about the program.

Biweekly amniocentesis and MSAFP follow-up sessions are available on-site. Genetic counseling services and translation services are available on an ongoing basis on-site as well. Special procedures such as chorionic villous sampling (CVS), fetal blood sampling, and medical genetic evaluations are available at the tertiary center at UCSF. The SFGH counselors and translators facilitate the provision of medical genetic evaluations, accompany the patients, and provide follow-up as needed. The DNA analysis and karyotyping for these patients are available through the cytogenetic and DNA laboratories at UCSF.

Of patients referred for services, 80% came in for counseling and follow-up procedures. The remainder either could not be reached, declined counseling, had a fetal demise, or had been counseled previously. Of patients with advanced maternal age, 58% had either amniocentesis or CVS. This represents a seven-fold increase in the acceptance of prenatal diagnosis in this patient population. All newborns with congenital anomalies received medical genetic evaluation, and all parents were counseled.

We believe a number of factors contribute to enhancing patient utilization of services. The provision of services in a familiar setting makes patients feel more comfortable, and the process of genetic counseling easier and less threatening. On-site services also make it physically easier for patients to present for services. Tying the new service into existing perinatal services allows for cohesiveness and a smooth referral system, as well as continuity in care.

The availability of specially trained and oriented translators is without a doubt one of the program's strongest assets. This allows for a gradual and smooth introduction of new medical technology to our population, while important cultural beliefs and practices are acknowledged. The program's translators not only allow direct communication with patients, they also help identify cultural beliefs important for culturally sensitive and meaningful genetic counseling. Another important factor is the counseling format. Lengthy and simple term counseling sessions are offered to patients and any family members who participate in the decision making. Our Chinese patients often involve their wise and elderly relatives in the decision-making process. Although patients are seen by appointment, an "open door" policy is utilized, and drop-in

visits are welcomed. Often patients stop by to see us following a routine appointment, or after they have had their babies, to clarify things that were not previously understood, to let us know how they are doing, to show us their baby, or to share concerns.

Services are provided free of charge. Approximately 90% of the patients seen by us for genetic counseling and testing did not have third-party reimbursement. The majority of these patients were funded through the grant's funds.

It is important to note that there are a number of difficulties in service delivery. The vast majority of patients do not request services, and are seen as a result of referral by a physician or nurse—a referral of which they are not always aware. Whereas in most other practice settings patients seek services, we sometimes "seek" the patients. In addition, the program's staff have the primary responsibility of contacting patients and scheduling the appointments. This task is time consuming since a significant proportion of patients do not have phones.

Serving medically unsophisticated and undereducated patients makes our education efforts challenging, not only because of information delivery, but also because our patients probably experience a higher level of anxiety than others with better educational backgrounds. Another difficulty in the area of education is that available materials about prenatal diagnosis and genetic counseling were found to be unsuitable for our patient population in terms of literacy level and linguistic needs. Although informative and meaningful counseling can be provided, transcultural linguistic and cultural barriers reduce the efficacy of counseling. When direct communication is not possible, some information gets lost on both sides, even when capable translators are being used. Introducing Western medical concepts to new immigrant populations is rather challenging. For instance, encouraging an active process of informed decision making can be difficult for individuals who are not used to making their own medical decisions. Also, concepts of birth defects and prenatal diagnosis are confusing to some of our patients because of deep-rooted cultural and religious beliefs.

In attempting to overcome the described difficulties, we needed to do the following:

- 1) Get to know our patients and identify their special needs;

- 2) Accept the cultural, educational, linguistic, and socioeconomic constraints on counseling;
- 3) Adapt the existing resources to better fit our patients' needs without sacrificing professional standards; and
- 4) Reconcile the ideal of the optimal counseling outcome with what was possible under the circumstances, and have more realistic expectations.

Overall, we have shown that by bringing down the barriers that keep individuals from receiving care, sophisticated genetic counseling services can be provided in a meaningful and informative way to multiethnic, undereducated, medically unsophisticated, low-income non-English speaking patients. Through their high acceptance of genetic counseling and testing services, our patients have demonstrated that the desire to exercise reproductive choice is not a function of ethnicity, education, or socioeconomic class.

There are other model genetic counseling programs for underserved populations around the nation. Many of us have demonstrated that barriers can be overcome when appropriate measures are taken. As we are funded by federal funds made available to promote innovations in care, our mission is complete when the goals of the project are accomplished. The irony of this, however, is that as we identify needs and find successful ways to address them, we become unable to function because of a lack of funding.

ACCESS TO HEALTH CARE

ELIZABETH WISDOM

In 1981, the President's Commission on Ethics in Biomedical Research concluded that society has an ethical obligation to provide health care. A report on access to health care, issued by the commission, stated, "Equitable access to health care requires that all citizens be able to secure an adequate level of care without excessive burdens."

While on educational leave from her former position at the Ohio Department of Health, Marshia Herring, an outstanding scholar of public health, conducted a study on these recommendations in 1983. Her study centered

around identifying barriers that impede access to health care from the institutional, provider, and consumer level. I have modified Marshia's paper to cover some solutions that my association has tried, along with some of my own general thoughts and comments.

A) Institutional Health Care: The Delivery System

- 1) Services and providers are unequally distributed. In the state of Ohio, only a half dozen pediatric hematologists specialize in the treatment of sickle cell disease.
- 2) This problem could be resolved by recruiting and encouraging more medical students to specialize in the field.

B) Unequal hours conflict with consumer work schedules.

- 1) Clinics should be encouraged to extend their office hours to at least two nights during the week and remain open on weekends until noon.

C) People get lost in the maze of facility requirements. Some clients are sent to several facilities for different services on different days.

- 1) This problem could be solved by establishing more one-stop comprehensive service centers, providing all the health services needed.
- 2) A well-organized case management system might improve service.
- 3) A well-oiled case management system might also serve to coordinate between the doctor, clinic, hospital and parent.

D) Poor follow-up causes lack of service or gaps in service. This would include breakdown in notifying the appropriate providers of test results. The U.S. mail admits to the loss of 5% in mail deliveries. Laboratories fail on at least 2%. The rest of the system cannot afford to add to these losses.

- 1) Our best solution, in my opinion, might be automating the state laboratory to prevent or decrease loss, and to track the path of test results from the time they leave the hospital.

E) Bureaucratic response to client needs is one of the surest ways to prevent access to service. The University Hospital in my hometown demonstrated a classic example of inappropriate response to clientele. Through the concerted efforts of the Sickle Cell Parents Awareness Group, the institution was forced to take corrective action.

- 1) Communication skills were improved.
- 2) Patient care was monitored frequently.

- 3) A parent was given a seat on the hospital advisory board.
- 4) Some of the nursing staff were transferred away from the sickle cell ward and reassigned to a different duty.
- 5) Patient/staff education was provided via in-service sessions.
- 6) Coordination and follow-up were improved.
- 7) "Quality Assurance" was instituted with the involvement of the Sickle Cell Awareness Group.
- 8) A good referral system was started.
- 9) The Parents Group established a meaningful relationship with adult clients.
- 10) A journal is kept on clients and reviewed for progress.
- 11) Consumer advocates include the Sickle Cell Awareness Group of Greater Cincinnati, the Ohio Sickle Cell & Health Association and the Children's Hospital Board of Trustees of the University of Cincinnati.

F) Consumer Concerns

- 1) In smaller towns, clinic locations are sometimes inconvenient. Transportation may be unavailable.
 - a) This problem might be changed by instituting regional centers.
- 2) Sometimes there is a stigma attached to seeking assistance.
 - a) Education and understanding would solve this problem.
- 3) Clients are sometimes referred to as "drug addicts" when seen at the emergency room, even in 1989. This is one of the oldest problems we have had to face and it still exists.
 - a) Training of emergency room staff would help stop this bias.
 - b) Education of the provider professional staff is seriously needed to improve attitudes. In-service training might help to increase cultural awareness and sensitivity to certain needs.
 - c) More public education to promote services via supermarkets, churches, radio, clubs, organizations, schools, etc.

The President's Commission on Ethics in Biomedical Research concluded by declaring that improving access or removal of barriers was a responsibility of the health care delivery system or "an ethical obligation." Yet access alone guarantees neither good outcomes, nor maximum use of health facilities.

WORKSHOP

A. LACK OF REFERRAL NETWORKS

LINKING ADDRESSERS OF DISEASE-SPECIFIC NEEDS

JUNE VAVASSEUR, M.P.H.

The title of this workshop is the "Lack of Referral Networks." I am a social worker and a health educator by profession. I worked for 26 years as a medical social worker at the Los Angeles County-University of Southern California Medical Center, and the last 12 of those 26 years were spent working with people with sickle cell disease and their families. I then served as the Director of Program Development at the National Association for Sickle Cell Disease (NASCD), which is a composite of local associations providing services for persons and families affected by that disease.

I am sharing my background with you to give you an idea of my experience in the area of referral networks. Having provided and/or located services for families as well as having assisted local groups in the development of educational materials, educational programs, and other needed psychosocial services, long ago came to understand the value of referral networks to patients, families, and professionals responsible for the delivery of medical and/or other services.

Often during my years at NASCD, I answered requests for information about the location of medical providers, social services, etc. When I could refer families or other service professionals to a local sickle cell group, they were indeed gratified. We also received many requests from persons in areas where there was no local group for assistance in developing a chapter. The services of such a nationwide network enhance life for persons and families affected by chronic medical problems.

For the purpose of our workshop discussion, I would like to offer a very general definition of referral networks. I see these networks as conglomerations of groups of persons affected by a specific disease, their families, other interested persons, and often some service professionals who come together out

of many needs, such as lack of information about the disease, lack of information about medical and/or service resources, or the need for emotional and/or social support. These groups engage in activities to meet these needs, i.e., fund raising, education, psychologic support for parents of affected children or for the affected persons themselves, social services, etc. The groups range from small, all-volunteer groups with limited membership, to large, formally structured organizations with paid professional staffs. Examples of the conglomerations of these groups or the networks are Little People of America, Spina Bifida Association, National Association for Sickle Cell Disease, National Hemophilia Foundation, National Down Syndrome Organization, National Tay-Sachs Foundation, etc.

In areas where numbers are minimal, some groups unite across disease lines with other small groups and form larger organizations, since the needs are similar regardless of the specific disease. Groups also unite across disease lines for the purpose of more visibility nationally for specific purposes, such as the Alliance of Genetic Support Groups.

The definition could be expanded to include an alliance with service-provider organizations. The previously referred to alliance is an example of this type of network also. But the basic idea, as I see it, is that a referral network should be designed to bring together groups that provide activities that meet the needs, and/or locate services that meet the needs, of persons affected with a chronic medical diagnosis. To reiterate, needs are medical and/or psychosocial and include financial needs, socialization needs, advocacy needs, housing needs, counseling needs, etc.

These networks, however, are not without problems. In the workshop today we would like to discuss the value of these networks and also the problems faced by them, such as lack of finances, membership, recruitment, program development, strategies for increasing visibility, obtaining support of medical and other service providers, "burnout" among leaders, and others that you may have experienced.

In conclusion, I would like to suggest that we focus on the statement of the problem as we listen to the other panel members share their experiences in their specific disease-oriented group. The problem statement and the issues that we are charged to discuss are as follows:

- Disease-oriented referral networks are lacking in some areas and often are underused and/or lack visibility where they are developed.
- What are the purposes of networks?
- What are reasons for lack of networks?
- What are reasons for lack of visibility and/or underuse?
- What are other problems faced by established networks?
- What are the attitudes of primary care providers toward these networks?

We also need to develop recommendations as a result of our discussion today. Some areas I might suggest for recommendations are:

- How to increase the numbers of referral networks.
- How to overcome the problems that networks face.
- How to educate primary care providers about the purpose of these networks and their value for the patients and their families.
- How to form alliances with service provider groups.

A PARENT'S PERSPECTIVE

JOANNE FOLTS MACKEY, R.N., B.S.N.

We are in a "communication age"—you've seen the ads. We connect with fiber-optic networks, fax machines, and computerized everything.

As I thought about the topic of this workshop, "Lack of Referral Networks," I realized that one of the most frustrating situations I had to face when our baby was born, was not having accurate information on which to base decisions. I had been away from nursing school for ten years and had no reason to be up-to-date on shunting, myelomeningocele, or neurogenic bladder treatment. There was no effective treatment for myelomeningocele and hydrocephalus when I was in school, and the prognosis for our child was poor. I called all the local resource agencies I knew—March of Dimes and the Health Department—but neither could provide information in less than a week. Our

decision to suspend care on our child was based on old information, and antiquated attitudes.

It took me a little more than two years and the use of the terminology *spina bifida* to discover some of the basic support systems I needed for our child and for our family. The resources were out there, but we were never given any information about them.

Today, my child just had his eleventh birthday, achieves in the upper level of his fifth-grade class, has had 11 major surgeries, is largely ambulatory, and as a disabled citizen has contributed to society already by being a positive force in his mainstreamed environment. But even after all these years, and my state and national level involvement in issues concerning disabled citizens, I still have problems finding information about the details of my son's care and equipment. He recently needed a new wheelchair. It took dozens of phone calls, two vendors, magazines, and conversations with other parents to arrive at a decision for a chair that would not be outdated before he used it! At least I knew all these people to call!

Families are thrust into situations often without notice, with little or no previous information. There are no "easy to assemble" instructions written clearly enough for the unexperienced to access care in the system. Often, the best resource is another parent one happens to meet at a clinic.

I work with young children with developmental disabilities and their families. Many of them never saw a list of "800" numbers, few have printed material on their child's diagnosis, and most have never accessed a "referral network" (some even said they would be reluctant to dial for fear they would sound "stupid"). An informal survey of parents attending a myelodysplasia clinic revealed the same attitudes. Are we meeting family needs or are we expecting them to respond to our system?

In preparing to speak to you today, I was handed three papers, two published in 1977 and one in 1981. I was thrilled and dismayed: Thrilled to know my own thought processes were validated, and dismayed to see the same problems brought up then as I think we see today, about 10 years later. But before we explore the problems, I think we need to define our term, *referral networks*, that we say we lack. (Notice the word is not *resources* but *referral*.)

Webster tells us that referral means to *send* or *direct* (a person) to someone or something for *aid*, *information*, etc. *Network* is defined as "any arrangement or fabric of parallel wires, threads, etc., crossed at regular intervals by others fastened to them so as to leave open spaces; netting; mesh." I would also point out that the "aid" information, etc., just mentioned can be described as resources. In other words, I would ask you to examine those interconnected means by which we direct people to resources.

I offer the following as food for thought in identifying the problem and suggesting the strategies and recommendations from this group.

In North Carolina alone, a listing of 33 statewide organizations is just a partial reflection of the resources available to our citizens. We have several statewide "800" numbers and a central resource line called "Careline." (Those citizens who require assistance with information rarely know this number's use.) Our new Central Directory Systems Staff has had difficulty accessing information on other state and national systems, not to mention resources within the state. Staff members know that these organizations exist, but are unable to "network" or interact in a direct way. The explosion of technology has made the concept of networking a real possibility—but where are we? Are we simply lacking the human collaborative efforts needed to make the linkages to form the mesh?

I would also ask you to consider the professional's awareness level of the resources available to respond to needs of families. Medical/professional schools traditionally offer little training, or place a low priority on the referral of families for resource information. Other professionals involved with the family usually have a piece of information, but rarely do they have the tools needed to access accurate information through the scattered available networks. The family's needs become a "victim of the system."

Add to this vast array of limitations, the parents' need for immediate, accurate, and comprehensive information. In the case of AFP screening, the time frame for decisions is less than three weeks. And in the case of a child with a genetic condition, long-term resource information about many phases of care must be accessed throughout a lifetime. *Decisions for a life* are made on information.

Our strategies and recommendations should take into consideration the impact of P.L. 99-457 and what it offers as a basis for networks. Technology is available and is now being used in parallel ways. Can we not expect that these already-established networks would work toward a collaborative consortium to form a readily-accessible information system?

As professionals and consumers, is it not our responsibility and that of state and local resource providers to inform both parents and professionals of what's out there? Some of us are in positions to influence program planning and policy so that professionals will become more aware of the needs of families and less likely to try to fit families into inappropriate already-existing services.

Last, we must ask if this information is available at all levels to those who need it, be it in a local clinic, regional medical center, state legislature, or House of Representatives. Massive public information about a true refund network must be examined.

Let us take time in this session to see how referral network pieces can be picked up and organized into an efficient "mesh" of information.

THE SPINA BIFIDA ASSOCIATION OF AMERICA: SUCSESSES AND SHORTCOMINGS

PATRICK SABADIE

I am a parent of a child with the birth defect spina bifida, a volunteer, and a naval officer. I am the President of the Spina Bifida Association of America (SBAA), which in the immediate past has been predominantly an information and referral network for parents, adults with spina bifida, and the professionals who serve persons with spina bifida. My own experience with this particular referral network is extensive.

Because I am in the Navy, I move around a good bit. We have lived in the following states over the 15 years of my son Mark's life: Mississippi, Rhode

Island, Florida, Texas, Maine, and Virginia. I do not recall how I first heard of the SBAA; however, it was in Mississippi right after my son was born. Over the years, I have contacted chapters in each state to gather intelligence on what to expect in the areas of care, treatment, and schooling. The peace of mind my wife and I had because we were able to contact other parents in the area was reassuring. A different kind of information was gathered from parents than was obtained from the medical professionals. Both types were necessary and complementary.

THE SBAA AS A REFERRAL NETWORK

The SBAA is a 17-year-old association of 10,000 members and 90 chapters. The national association was formed in 1972 when some 12 chapters came together in Chicago under the auspices of the Easter Seal Society. The chapters that make up the network are all very different from one another. The range of programs and the levels of sophistication vary significantly. Standardization among chapters or control of chapters by the national association is difficult, as the interests and the needs of the individual chapters are different.

The primary thrust of the SBAA since 1972 has been to increase public awareness of spina bifida and to provide accurate and up-to-date information to families living with spina bifida through our Information and Referral Program.

Some areas of the country are well covered by chapters and some areas, including entire states, are not. Chapters are normally associated with a major medical treatment facility, where usually there is a multidisciplinary clinic for the care of persons with spina bifida. Most of the 220 clinics with which the SBAA is in contact are geared to the care of children. However, because of the 90% survival rate of persons with spina bifida over the last 15 to 20 years, there is a growing population of adults with spina bifida that are being overlooked by the medical profession. This population represents a significant and growing group that must be plugged into a network that is not dependent on parents.

Since there are about 90 chapters and 220 clinics, not all clinics have an associated SBAA chapter. Some chapters have members that are seen in two or three different clinics. Almost every facility that routinely sees children with birth

defects or other diseases has a parent support group of one kind or another, either disease-specific or of a more general type.

If we look at the SBAA and its chapters as a referral network there are many good and bad features. The good features are the significant strengths of the SBAA and other disability groups. Some of these features benefit the consumer and some benefit the providers. The good points are that the SBAA is:

- Nationwide;
- Staffed with committed volunteers;
- Supplied with accurate information, including information about maternal serum alpha-fetoprotein (MSAFP) screening in the case of spina bifida;
- Aware who the caring and medically current care providers are;
- Aware of school systems and other local support services;
- A forum for the cross-pollination of ideas. The best programs and techniques from all areas of the country are spread around through SBAA publications and national meetings; and
- A tool which professionals can use to pass information to a large body of interested consumers.

The problem areas associated with a primarily volunteer group of individuals are listed below. The SBAA suffers from all of these problems:

- 1) **There is a wide variety of competence and capability in chapters.** Some areas have multiple chapters, whereas other states have none. Some chapters cover a whole state. Some chapters have offices and a staff. However, most are run out of someone's home. Some chapters are run as a personal fiefdom by a zealous, opinionated individual. Most chapters have leaders who are competent, caring and conscientious, but few in number.
- 2) **There are holes in coverage of the country.** There are some 220 clinics treating persons with spina bifida, but the SBAA only has about 90 chapters. Ideally, there should be a chapter working with each clinic. There will probably be some type of parent support group functioning

with each clinic, either disability-oriented or of a more general nature. At some medical treatment facilities, there is a staff professional who works with parents. The formal establishment of a chapter of the SBAA would impact negatively on this person's job. Therefore, this person is not interested in forming a chapter.

- 3) **Poor rural area coverage.**
- 4) **Lack of credibility of chapter personnel with providers.** This can be cured only through a good rapport between the professionals and the consumer. Knowledge standards and some sort of certification would have to be considered.
- 5) **Lack of acceptance by providers of parent/patient role in the treatment process.**
- 6) **Widely varying levels of leadership, managerial, and communication skills in chapter leaders.** Unemotional, unbiased input would have to be provided by the consumer.
- 7) **No depth of talent or organized succession system on which to fall back when burnout strikes the leadership of a chapter, or the leadership moves, quits, dies, gets angry, etc., and is no longer involved.**

Genetics is merely a piece of the pie for a chapter, and not necessarily a large piece. Genetics becomes increasingly important, however, as the population with spina bifida ages and wants to have children. This issue opens many ethical and personal belief issues that may be divisive within the chapter or family. Until now, the SBAA and its chapters have been reacting to births, after the time when genetic issues would have been raised. The emergence of MSAFP testing is significantly increasing the interest of the chapters in genetic issues. Also, now that 90 to 95% of persons with spina bifida are living, they want to marry and have families, and genetic services are definitely in order. We have a large population of teenagers who will become adults in the next five years, and the number is growing. The medical community in general is not prepared to deal with an adult population with spina bifida.

The genetics field is probably the best prepared of all the medical subcommunities.

METHODOLOGIES FOR OVERCOMING THE PROBLEMS

Most of the methodologies and recommendations that I will present are based on the assumption that the concept of parental/patient involvement in the care and treatment of the problem is accepted by the providers.

- 1) Use the clinic staff, in the person of the social worker or the nurse, to educate chapters on their roles. Make this education part of someone's job.
- 2) The hospital of birth must play an active role in the referral process. In the case of spina bifida, the referral to a major medical center where appropriate treatment is available must be made immediately. My story is that our son was born in the county hospital in Mississippi, 85 miles from Memphis, where he was sent on the tenth day and referred to a neurosurgeon. The county hospital personnel knew what Mark had, but they did not know how to treat spina bifida because he should have been seen immediately at birth by the neurosurgeon. Fortunately, there seems to have been no aggravation of his condition due to the improper and unaggressive treatment at birth. The most effective source of help for my wife and me at this time was another ex-Navy family to whom the L.P.N. at the hospital in Memphis referred us.
- 3) The treatment facility needs to support the chapter. Especially important is the time-consuming and relatively cheap logistical support of meeting space; office space for files; equipment and a desk; mail services; copying facilities; telephones; etc. The clinic should provide training to the chapter's outreach team so its role can be filled by trained, competent persons with whom the clinic staff can be comfortable. Our most successful chapters are the ones with the closest ties to clinics.
- 4) Allow the trained chapter team to participate in the clinic visit process.
- 5) Support the creation of requirements for continuing education with parent support groups serving as a referral source and as a valuable part of the whole treatment team.

EDUCATING PRIMARY CARE PROVIDERS

The following suggestions should be implemented if providers are to enjoy the fruits of a fully equipped and fully staffed treatment team that includes the parent/patient.

- 1) Establish requirements for continuing education for providers that delineate the role of the parent, networks, etc.
- 2) Publicize success stories in the popular press as well as in the journals.
- 3) Have providers identify the parents who can fit in, and nurture and train them to fill the role.
- 4) Export the model to other areas if a positive contribution is identified.

In summary, the SBAA, like many other disease-related associations, can and does form a very effective referral network. Connecting with the chapters and with other parents has and will continue to be extremely valuable to me and my wife.

WORKSHOP

B. PROVISION OF SERVICES TO ISOLATED POPULATIONS

THE UNIQUE CHALLENGE OF ISOLATED POPULATIONS

JOAN FITZGERALD, M.S.

Isolated populations present a unique challenge for the genetic service-provider since isolation may occur due to many factors. Barriers may exist despite the availability of services in a particular geographic region; even in large metropolitan areas, individuals may feel excluded from services several blocks away due to their perceptions, attitudes, etc. However, individuals isolated for rural and/or geographic reasons present a particularly formidable challenge to the genetic practitioner.

Barriers to providing genetic services to these individuals generally encompass issues of limited accessibility complicated by attitudinal differences. Accessibility is a major component since communities may be small, separated by vast distances, and with no available mass transit system or even an adequate number of paved roads. This presents a financial concern for the genetic professional since he/she will waste a large amount of time just getting to genetic outreach clinics to provide services. Conversely, since most needs for services are not acute, clients will not travel to a genetic center in another part of the state, and thus will not receive services unless local service is available. For the practitioner, community isolation obviates long-distance follow-up, complicates or disallows specimen shipment for laboratory study, and necessitates seeing many clients on a given clinic day. Communities may not have adequate health care facilities to accommodate recommendations for additional studies like skeletal survey, magnetic resonance imaging (MRI), developmental testing, etc., requiring complex coordination of rare in-state services with testing only accessible in another state. Since general medical services may be difficult to maintain, providers tend to move frequently into and out of the area; follow-up and coordination responsibilities must be assumed by the genetic personnel or they will not occur. This may result in unnecessary delays and potentially

tragic outcomes for families unfamiliar with the methods necessary to negotiate complex testing and/or management recommendations.

Although seemingly every detail has been addressed and arrangements for services secured, an unexpected snowstorm can postpone a clinic, cause numerous scheduling programs, and result in a large number of cancelled appointments.

The general attitudes of rural populations toward genetic services may be quite different from those of their urban counterparts. These individuals may:

- 1) Feel genetic services are unnecessary because there is no immediate concern;
- 2) Equate genetics with abortion, eugenics, government regulation, research, or teaching;
- 3) Perceive no need for services unless recommended by their primary care provider;
- 4) View genetics as having no financial benefit;
- 5) Engage in lifestyles characterized by folklore and bizarre explanations for genetic conditions;
- 6) Participate in maintaining damaging family secrets;
- 7) Receive late or no prenatal care so that prenatal diagnosis becomes difficult; and
- 8) Choose to utilize services only if affiliated with a major university center because "bigger is better."

Finally, many people living in small communities have "escaped" from large metropolitan areas to avoid a health care system they see as unfriendly.

These attitudes then have an impact on the clients' willingness to avail themselves of services; since their livelihood (e.g., farming) may interfere with the ability to keep appointments, late arrivals and cancellations are not uncommon. Specific seasonal restrictions exist and there may be dramatic fluctuations in their financial situation. Many clients do not tolerate lengthy evaluations and may be highly suspicious of genetic consultation protocols since exposure to these policies does not generally occur in rural settings. There is a greater dependence on extended family for emotional support, necessitating co-

ordination of many schedules to insure that all relatives can attend clinic. Of interest is our observation that rural populations often view time and the concept of being "on time" differently from other populations; if the appointment is at 9:00 am, they will show up "around" 9:00, which may be anywhere from 8:00 to 10:00 depending on how the genetic appointment happens to fit in with their agenda on that particular day.

The attitudes of the rural medical community are similarly different from university-based practitioners. In the rural medical community, educational initiatives are poorly attended and misinformation is widespread. Existing referral patterns for other medical services dictate where practitioners will refer for genetic consultation, resulting in unnecessary travel with consequent delays in diagnosis and counseling for their patients. The concept of diagnosis versus counseling is poorly understood with "counseling" viewed as unnecessary and trivial. Finally, rural health care providers, like their patients, also have escaped from urbanized medicine and view genetic specialists as "university types" who are not to be trusted.

In summary, the provision of genetic services to isolated populations presents a unique challenge for genetic professionals who must often overcome geographic and climatic barriers to reach the populations in need of their specialties. The greater challenge lies in addressing and overcoming long-existing, ingrained attitudes of both the client population and the medical community. Although these attitudes may seem insurmountable, effective services are possible if the genetic community is willing to take the time to solicit specific data about their target population and structure the delivery system to address these parameters.

PROVISION OF SERVICES AT THE FORT PECK INDIAN RESERVATION

SPIKE BIGHORN AND ROXANNE BIGHORN

When discussing the isolated population of our area (northeastern Montana), the discussion must eventually center on the Native American population residing on the Fort Peck Indian Reservation. Not only are they some-

what isolated because of the boundaries of the reservation, but they suffer considerable isolation due to racial factors and attitudes. This is not to infer racial bias, but to state the simple fact that there is going to be a certain amount of misunderstanding and stereotyping whenever two distinct races of people reside in the same area.

The Fort Peck Indian Reservation, home to the Assiniboine and Sioux tribes, suffers an unemployment rate of approximately 40%. Although much higher than the national average, this rate is far lower than that suffered by other tribes in the nation. Many reservations suffer unemployment rates that climb over 90%. The Fort Peck Reservation is fortunate to claim two industries that offer employment opportunities to an estimated 550 workers during peak production seasons. Because of the economic stability of the reservation, the Fort Peck tribal members enjoy an adequate supply of jobs when they seek employment. Furthermore, this stability makes the Fort Peck tribes the exception rather than the rule when discussing Indian reservations. Nevertheless, the reservation boundaries, and its location, would categorize the tribal members who reside there as an "isolated population."

In relation to the major population areas of Montana, the Fort Peck Reservation is indeed isolated. To travel to Billings, the largest city within the state, one resident must drive five and one-half hours. When traveling to Great Falls, the second largest city, a resident must drive six hours. To travel to the state university in Missoula, a resident must be willing to spend nine hours on the highway. In case the individual is not fond of driving, the commuter airline that serves the reservation consists of a fleet of seven-seat, twin engine Cessnas. To travel to any of the three cities named earlier, a traveler should be prepared to pay in the range of \$190–360 for a round trip ticket. There is no bus line that serves the reservation. The nearest bus terminal is 100 miles away. Although these factors are out of the control of genetic professionals, it is important to mention them as they are a huge deterrent to travel to and from the Fort Peck Reservation. Pleasure trips are made unpleasant by the isolation, so one can understand how difficult trips can be for health and business reasons. Because of the isolation, many residents are unable to consult genetics professionals in the major population areas of our state. They are unable to seek these services because of a lack of funds and a lack of transportation.

Additionally, isolated populations are somewhat intimidated and distrustful of doctors and other health care professionals. On the Fort Peck Reservation, this is ingrained in some of the tribal members by the stories handed down through the generations concerning the treatment of their ancestors by the non-Native Americans. Although many have come to respect and trust the local doctors that staff the Indian Health Service (IHS) clinic, they become introverted and distrustful when they are referred to the health professionals off the reservation. There are countless instances where tribal members do not consult these health professionals until they are in a life or death situation. One solution to alleviating this problem is to periodically set up clinics on the reservation to treat the illnesses and conditions that exist there. By bringing their services to the reservation, the health professionals would build a trust between their offices and the local tribal members. Moreover, by conducting the examination while being accompanied by the patient's IHS physician, the visiting professional would be granted instant credibility and cooperation by the patient. This may be expensive to the particular health professional, but it would ensure that individuals who are members of isolated populations could receive the best health care possible without leaving the reservation. Obviously, some health problems are so major that the local facilities will be unable to handle the treatment prescribed. However, clinics such as those conducted by geneticists could be mobilized and moved onto the reservations for short periods of time.

In our particular case, we sought genetic services because of our infant son's health problems. We consulted Dr. Susan Lewin from Shodair Children's Hospital in Helena, Montana. Our initial consultation occurred during May 1988 in Billings. As stated earlier, we had to drive five and one-half hours to keep our appointment there with Dr. Lewin. Our second visit took place at Dr. Lewin's office in Helena. The travel for the second visit was by air, because the driving time to Helena is seven and one-half hours. The round trip ticket for one person was \$215.00. The total cost we incurred for these two visits, which is minimal compared to the health needs of others, was approximately \$400.00.

We are very fortunate, considering the fact that both of us are employed, and can rely on a regular paycheck to offset the costs we experienced. However, for those residents who do choose to seek health care off the reservation, they often

have inadequate financial resources to pay the costs of the trip. Again, a mobile clinic would ease their financial burdens, and allow them to get their health care needs addressed.

Receiving authorization for a mobile clinic to visit a reservation is simple. By cooperating with the local Indian Health Service, tribal government, and local hospital, the mobile clinic can ensure the assistance of these local government agencies and health care facilities. For example, an ear, eye, nose, and throat specialist from North Dakota just completed an 18-year relationship with the Indian Health Service at the Fort Peck Reservation. The ear clinics were held each week, and the specialist had appointments scheduled from 8:00 a.m. to 5:00 p.m. He was of great benefit to the care of those children on the Fort Peck Reservation who suffered from ear problems. As you can see, the model for a mobile clinic is in place and is familiar to the physicians on the Fort Peck Reservation, and is well established with the tribal members in the area.

In summary, the easiest solution to offsetting problems in providing services to isolated populations is by taking these services to the affected areas. This may prove expensive, but is well worth the effort when considering the fine services the clients receive; services many of them were never able afford, or didn't seek due to cultural differences and misunderstandings. Finally, these services seem to be utilized by a great number of children. The majority of health professionals will spare little expense when the care of children is involved. What links the health professional with the members of the isolated population? The provision of quality health care to the children in these isolated regions. Children are held in the highest regard by members of all races. This would be the middle ground for all parties to share when negotiating mobile clinics, or when urging the isolated population to seek the services being provided by off-reservation health professionals. If this neutral ground can be found, then a lot of present concerns could be alleviated.

WORKSHOP

C. FINANCE/INSURANCE ISSUES

COMMON THEMES AMONG DIFFERENT TYPES OF INSURANCE

REED E. PYERITZ, M.D., PH.D.

Begin a conversation about medical care with any randomly selected lay persons and the discussion inevitably turns to insurance. Problems with the fragmented and everchanging system (perhaps "system" is too generous a word) of paying for health care expenses are legion, and no segment of American society is unaffected. Two workshops during this symposium addressed insurance issues from the consumer perspective, and a wide range of important barriers to adequate coverage were identified. This paper provides background for these workshops, a brief review of recent literature, and summary recommendation about how to obtain and retain various types of insurance.

DIFFERENT TYPES OF INSURANCE, COMMON THEMES

All types of insurance, including health, disability, and life, are of particular concern to patients and families with hereditary disorders. From the consumer perspective, several themes are common to all types; recognition of these themes early in a person's experience with the insurance industry will facilitate all subsequent interaction.

First, insurance companies are woefully ignorant about hereditary disorders. Obviously they are most concerned with the major causes of morbidity and mortality in society, and even produce respected and useful data on life expectancy and its association with certain attributes, such as weight and blood pressure. As illustrated by the HIV epidemic, the industry can respond to new challenges quite aggressively and concertedly. When an insurance company encounters an applicant with an uncommon condition, the point of contact at the home office is a nonphysician employee, who accepts or rejects the application on any of a variety of criteria, but almost never on detailed, contemporary understanding of the rare disorder. There is little experience with bringing insur-

ers up to speed regarding a rare disorder at the time of initial application—in effect, prophylactic education. If a particular policy is highly desired, however, appeal of initial rejection should be pursued. On appeal, any information provided by the applicant and medical experts can be effective.

Furthermore, the chances increase that the appeal will be reviewed by a physician employee of the insurer. Although the likelihood that such a physician will appreciate that “hereditary disease” should not be equated automatically with catastrophic problems, disability, or shortened life expectancy has not been explored, so clearly the chances for a more reasoned response are increased.

Second, all information supplied on application and the disposition of applications are subject to permanent storage in data banks; most insurance companies have access to this information. One of the largest such banks (the Medical Information Bureau) was commissioned by the Health Insurance Association of America, an umbrella organization for private insurance companies. Thus, while honesty is essential in answering questions, it is equally crucial to supply only the necessary information and to avoid arousing suspicion. A corollary is to avoid indiscriminate or premature application; anticipate how questions on the application should be answered, whether a physical examination will be required, and whether medical records can be accessed. On the other hand, there are times when haste will be advantageous, such as submitting an application before a diagnosis is secure; while especially important for young children, this strategy can be essential for adults with potential inherited susceptibilities or late-onset disorders.

Third, policies that seem similar in major characteristics, such as term, premium, and death benefit, vary widely in details, such as exclusion and waiting periods. Read all of the fine print, and seek help in understanding all of the nuances so that comparisons among plans can be accurate.

Fourth, group policies are almost always an economical, secure, and uncomplicated solution to insurance needs. Although group plans through employer benefits are by far the most common sources, professional, fraternal, and other organizations are arranging group plans more frequently. If employed by a business with more than 20 workers, federal statute prohibits discriminatory pricing of premiums in group policies on the basis of anticipated higher expen-

ditures. One drawback of employer-based plan is that a subscriber may become locked into an undesirable occupation because of the favorable benefit package. For employers of more than 20 people, an employee who leaves or is terminated for other than disciplinary reason is covered by the federal COBRA law, which provides identical insurance for 18 months if the ex-employee assumes the full cost of the premium. However, before leaving an employer, most people with an hereditary disorder, or with an affected dependent, are well advised to be certain that they have a new job with a group insurance package equal to or better than their current one.

Fifth, because of the complexity and changeability of the insurance system, self-education is essential. Support groups need to assume a more active and visible role in this regard; some already provide exceptionally comprehensive advice and assistance. The proceedings of this symposium are a starting point for preparing information booklets for consumers. But due to the marked variation in insurance plans among states, information must be modified for local requirements and must be revised periodically.

Finally, these issues are not benign, and the environment should be viewed at best as competitive, and at worst, hostile. Most insurers are interested in maximizing financial performance, and will respond predictably if loopholes are discovered in their policies. Hence, support groups, advisors, and workshops, such as this one, should temper their understandable enthusiasm for disseminating widely methods for "beating the system." Discretion may prove the wiser course.

HEALTH INSURANCE POSES SPECIAL PROBLEMS

According to a recent census bureau survey, up to 37 million American (14% of the population) had no public or private health insurance in 1988. And while the most common source of health insurance is through an employer, two-thirds of the uninsured were employees and their dependents. These data are being widely touted in the press and by politicians as the strongest indicators yet for the need for drastic, national reform of health insurance.

Unquestionably, people and families with hereditary disorders occasionally face special problems, and should always have a heightened concern in acquiring and maintaining adequate health insurance. Some of these problems are detailed

in the "Barriers" section of the workshops' reports, and others will be noted presently. But to what extent is health insurance deficient among consumers with hereditary disorders? The answer is unknown; few studies have addressed a long list of important economic issues surrounding hereditary conditions [1,2]. Little is known about direct and indirect costs of medical care, effects of disorders on earning potential, discrimination in purchasing insurance, and what constitutes adequate insurance. Such information can only be gained through rigorous sampling of a defined population; such studies are expensive to perform well, and funding agencies have been reluctant to support them.

When pilot studies have been conducted, the results have been helpful and somewhat surprising. For example, during 1988, the National Commission on Orphan Diseases (not all of which are hereditary disorders) surveyed by telephone 801 patients and caregiver-relatives and found the following. The rare disorder directly caused financial hardship in 43% of the sample, in part due to medical insurance covering only part of the medical expenses. Only 9% lacked any health insurance (less than the national average), while an additional 7% had policies that excluded the rare disorder from coverage. We were recently supported by the National Neurofibromatosis Foundation to survey adults with type I neurofibromatosis (NF-I) about the costs attributable to the disorder and their health insurance coverage [2]. In a sample of 56 individuals, out-of-pocket expenses for 1987 varied widely, from nothing to \$5000, with most under \$250; 11% had no health insurance, a rate not different from the nation as a whole; half of those uninsured were employed. This study needs to be expanded, and many other disorders need to be surveyed, in order to obtain objective data upon which to base lobbying and counseling.

Health maintenance organizations (HMOs) have achieved considerable presence in a short period of time. With few exceptions, HMOs have not resolved (or even considered) how to deliver genetic services. At the present time, few HMOs believe themselves large enough to support full-time geneticists and genetic laboratories; referral to professionals outside the plan is expensive, and can be viewed as a drain on potential profits. Prospective subscribers to HMOs need to be certain that the needs of genetically affected individuals will be attended to satisfactorily before signing a contract.

Many children with a hereditary or congenital condition are covered by state plan (often called Programs for Children with Special Health Care Needs), supplemented by a parent's health insurance policy. Both sources usually disappear when the child reaches majority or, in the case of family health insurance, ceases to be a full-time student. While some states are working toward extending coverage or providing a narrow window of opportunity for a young adult to buy into their parents' policy, this remains an age of high vulnerability. Consumers need to become more aware of these problems and to be counseled in advance.

In most instances, people who have serious medical problems should apply for disability in advance, and reapply if they are initially refused. If granted, they will be eligible for coverage under the Medicare program. Similarly, people who reach age 65 (or younger in some instances) become eligible for blanket Medicare insurance.

The health insurance problems of people with hereditary disorders occur primarily between the ages of 21 and 65. In the absence of universal health insurance, the merits of which are hotly debated [2-4], what options are available? People who meet the strict income and asset standards are eligible for assistance administered by the states and often called Medicaid. Medical assistance is also a viable option for some children who reach majority and are no longer covered under a parental policy; as long as the parents do not sign as a guarantor for their child (on an emotional level, an admittedly difficult step to take), the child may meet the poverty guidelines and be eligible for state assistance, even though the parents are financially well-off.

As noted above, most uninsured Americans are employed; while poor in many senses of the word, most are not so financially poor as to qualify for Medicaid. In many states, people not qualified for group policies, nor eligible for public assistance programs, can take advantage of state-mandated programs that provide health insurance for anyone—albeit at a surcharge to the average premium—and often with larger-than-average copayment requirements and deductibles. In some states the program is called “CHIP” (comprehensive health insurance plan), while others term it an “open enrollment period.” Some states have a “high-risk insurance plan” for individuals who have been denied on account of illness. Not only do the benefits of these plans vary widely, but some

exclude pre-existing conditions; in this latter case, a person would be covered for everything except their hereditary disorder. Worst of all, however, 16 states lack any such provision. The state insurance commissioner's office is the first place to call for specific details.

DISABILITY AND LIFE INSURANCE CAN USUALLY BE OBTAINED

Our study of NF-I showed that most adults with that disease do have some life insurance, usually through their employee benefits. For those without this option, the open market is not as hostile as it might appear. For example, policies for relatively small premiums—less than \$25,000 or \$50,000—often do not require a physical examination or much disclosure. To emphasize a point made above, shop around discretely before taking an inordinate risk of having a denial irretrievably embedded in a data base.

LEGISLATIVE INITIATIVES ABOUND

On the federal and state levels, keeping up with legislation introduced, let alone passed, that affects insurance coverage is a full-time job. In this area, support groups, especially umbrella organization such as the National Organization for Rare Disorders (NORD), perform valuable services. Not only do they let consumers know about new, advantageous programs, but they identify pending legislation that would benefit from effective lobbying. Contact NORD at P.O. Box 8923, New Fairfield, CT 06812 to join and be placed on the mailing list.

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MEDICAL FINANCIAL COUNSELING PROGRAM

DAVID R. LINNEY

The complexity and lack of uniformity in health care reimbursement makes it very difficult for patients to access, utilize, and maximize available third-party reimbursement.

There are many different third-party payers, including Blue Cross, private health insurance, state high-risk insurance plans, and a number of government assistance programs. Most have different eligibility requirements, application processes, covered medical services, and benefit payment levels. In addition, with the growth of health maintenance organizations (HMOs), preferred provider organizations (PPOs), and cost containment, many plans have managed care requirements (pre-authorizations, referrals, etc.).

For reimbursement to occur, information must be communicated between patients/families, insurers, and providers. Patients/families must play a role in the reimbursement system. Many have difficulty with the following:

- obtaining insurance;
- understanding provider bills;
- understanding insurance coverage and how to use insurance coverage;
- managing to make provider payments;
- knowing when and how to apply for available payment resources;
- knowing how to coordinate insurance coverage in the event of a job change or termination of insurance coverage; and
- obtaining HMO referrals and special insurer pre-authorizations.

The underserved often have greater difficulty understanding their reimbursement options and obtaining reimbursement because of cultural, language, educational, and economic barriers.

Compounding the complexity of reimbursement for genetic services is generally poor third-party coverage for these services. The main problem is that genetic services as such are not coverable as a separate service by third-party payers, while "genetic" physician services, diagnostic laboratory services, and special procedures like amniocentesis are covered by third-party payers. These procedures are covered not because they are genetic services but because they fall under other covered service categories (i.e., "physician," "diagnostic laboratory," or an "approved procedure"). Specialized genetic services such as genetic screening, genetic counseling, and evaluation of relatives are not generally covered.

What can be done to improve genetic services reimbursement for the underserved?

Overall reimbursement for genetic services needs to be improved not just for the underserved but for all citizens. Non-covered genetic services need to be covered. To effect this objective, CPT codes need to be expanded to include more genetic services and insurers will need to include genetic services as a covered policy benefit. A national effort to develop, promote and coordinate the expansion of coverage for genetic services needs to be undertaken.

The underserved can obtain more extensive use of existing reimbursement for genetic services now. Recommendations to better utilize reimbursement follow:

1) Providers of genetic services should:

- A) Assess genetic services coverage provided by major payers (Blue Cross, private health insurance including HMOs and PPOs, state high-risk plans, Medicaid and Medicare).
- B) Correlate coverage (and actual reimbursement received) for different genetic services charged by the provider.
- C) Determine if the provider can bill differently to better maximize reimbursement.

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- 2) Providers of genetic services should develop a network of payment resources for patient referral.
- 3) Providers of genetic services should assess each patient's insurance coverage and medical costs, and refer patients to available payment resources so that third-party reimbursement can be maximized and patient out-of-pocket expenses kept to a minimum.
- 4) Providers of genetic services should provide patients and families with consumer health insurance education in their primary language, from the appropriate cultural perspective, so that they can be informed about important insurance issues—need, availability, plan options, coverage limitations, and reimbursement coordination.
- 5) When appropriate, providers should work aggressively with third-party payers to coordinate coverage for genetic services for maximum reimbursement:
 - A) Referrals from HMOs need to be obtained prospectively.
 - B) Contract agreements or agreements of understanding with HMOs should be sought (based on payer mix for clientele served).
 - C) Contacts with third-party payers should be established, information about genetic services should be provided, and maximum payment for genetic services should be sought.
 - D) If third-party payers either inappropriately deny benefit payments or make inappropriate partial payments for genetic services, then providers should follow-up with the third-party payers to assure maximum reimbursement. Providers should be available to advocate for patients when Social Security disability benefits have been "inappropriately" denied and when grievances need to be filed with insurers.

I have developed a new area of health care, Medical Financial Counseling. The model itself (or an adaptation) might be valuable to better utilize existing reimbursement for genetic services for the underserved. Medical Financial Counseling is a health care patient service program that has been designed to

provide appropriate management for patient/family medical costs and related concerns.

It is systematic and prospective in its approach. The goal of a successful Medical Financial Counseling Program is to provide maximum insurance coverage and maximum reimbursement for patients/families so that patient/family out-of-pocket expenses are kept to a minimum.

There are four parts to the Medical Financial Counseling Program: I. *Financial Assessment*, where patient/family health insurance, medical costs and (if need be) financial status are assessed; II. *Patient Education*, where the patient/family is provided with information about insurance, medical costs, and available payment resources; III. *Reimbursement Coordination*, where reimbursement is coordinated and maximized and problem bills/insurance payments handled; and IV. *Special Advocacy*, where Social Security disability appeals, insurer grievances, and employment discrimination complaints are reviewed and advocacy is provided.

A summary of the Medical Financial Counseling Program follows. It includes a listing of "Common Consumer Health Care Financial Problems/Concerns."

COMMON CONSUMER HEALTH CARE PROBLEMS/CONCERNS

1. How do I pay for medical services which often cost thousands of dollars per year?
2. Can I obtain health insurance? What do I need to know about health insurance?
3. What payment resources are available if I need help paying my medical bills?
4. How do I deal with problem bills and insurance payments?
5. How do I coordinate insurance in the event of a job or insurance change or a change in dependent status?
6. What do I need to know about life insurance?
7. Should I inform a prospective employer that I have a medical condition?

**GREAT LAKES HEMOPHILIA FOUNDATION'S MEDICAL
FINANCIAL COUNSELING PROGRAM**

Medical Financial Counseling—consumer health care financial counseling service which provides for the management of patient/family medical costs and concerns.

I. Financial Assessment (special forms)

- A. Health Insurance
- B. Cost
- C. Financial Status

II. Patient Education

- A. Medical Costs
- B. Review of Patient Insurance Plan Benefits
- C. Patient Out-of-Pocket Liability
- D. Health Insurance Plan Information (Blue Cross, Commercial Insurance, Medicaid, Medicare, state high-risk insurance plans)
- E. Other Health Insurance Information (availability; plan options; managed care including HMOs and PPOs; COBRA; questions to ask a prospective employer; coordination in the event of a job or insurance change or a change in dependent status)
- F. Available Payment Resources (Welfare-AFDC, General Relief, Medical Assistance; Social Security—SSI, SSDI, Medicare; State/Title V Children with Special Health Care Needs; Division of Vocational Rehabilitation; State-legislated categorical disease programs)
- G. Provider Billing and Insurer Payment Procedures
- H. Life Insurance
- I. Rights to Employment and Discrimination

III. Reimbursement Coordination

- A. Follow-up with provider patient accounts departments, insurers, and other third-party payers

- B. Coordinating, Maximizing, and Increasing Reimbursement (using more than one third-party payer; maximizing insurance plan benefits including payer contact, special labeling, and medical letters; pre-authorization of benefits requests; expansion of benefits request)
- C. Referrals to Available Payment Resources
- D. HMO Referral Coordination
- E. Managed Care Certification Coordination

IV. Special Advocacy

- A. Social Security Disability Appeals
- B. Insurer Grievance Procedures
- C. Employment Discrimination Complaints

A STUDY OF MEDICAL COSTS ASSOCIATED WITH SELECTED GENETIC DISORDERS IN TEXAS

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The initial goals of this study of medical costs associated with selected genetic disorders in Texas were to quantify the medical costs associated with selected genetic disorders in Texas. In addition, we wished to ascertain the characteristics of the patients receiving services in terms of the types of services being delivered and the geographic distribution of patients and services. Much of the work on the geographic distribution of patients and services is described elsewhere in the proceedings of this Symposium (See "Needs Assessment for Genetic Services in Texas"). This study was undertaken as one of the activities of the Interagency Council for Genetic Services (IAC), which interfaces be-

tween the Texas Genetics Network (TEXGENE) and the Texas State Legislature. Eleven disorders were selected for investigation: cleft palate, congenital heart defects, cystic fibrosis, Down syndrome, hemophilia, muscular dystrophy, neurofibromatosis, phenylketonuria (PKU), sickle cell disease, spina bifida, and thalassemia/Cooley anemia.

It was felt that the scope of this study must be limited, since there was no central resource that would permit quantification of all medical costs for all patients with genetic disorders. The data sources would have to be readily available and broad in coverage. Two data sources were identified, Medicaid and the program for Chronically Ill and Disabled Children (CIDC).

We considered the limitations and advantages of both of these data sources. The limitation of Medicaid was that it covered only persons of low income (up to 125% of the federal poverty level during the period of the study). The advantages of this data source were that it represented a large share of total governmental expenditures for health care in Texas, and that it covered a broad spectrum of care, including acute care (inpatient and outpatient services) and long-term care (nursing homes and facilities for retarded citizens). The CIDC program covered children and young adults through age 21 with certain chronic or serious ailments, including many genetic disorders. This program was formerly known as the Crippled Children's Program. CIDC coverage included medical treatment, durable medical equipment, and rehabilitation. Its limitations were that it was the payer of last resort and the data would pertain only to the poor of Texas (up to 200% of the federal poverty level during the period of the study). Its advantage was that it was funded by state dollars and, therefore, would be of interest to the state government.

Overall, we recognized from the outset that the limitations of this study were: 1) it would focus primarily on the indigent; and 2) it would not quantify the costs of all medical care for the poor, such as that provided by city and county hospitals and governments, medical schools, and private health care providers (i.e., unreimbursed care).

The strengths of this study were that it would give conservative estimates of medical costs, that it included the broad spectrum of medical care covered by Medicaid and CIDC, and that medical costs of these agencies would be of

special interest to the state government and the state agencies represented on the IAC.

MEDICAID STUDY

The study period for the Medicaid data was April 1, 1987, through December 31, 1987. The beginning date was constrained by the availability of diagnosis related groups (DRGs) data that was important to the analysis. The ending date was constrained by the time-period for Medicaid claims processing, which was typically six months, and the fact that we were undertaking this study in late spring of 1988.

One of the issues that was important for us to consider was the amount paid versus the amount billed under the Medicaid system. The amount paid represented the actual governmental expenditures, and was considered an underestimate of the cost to the insurance carrier or the individual. The amount billed may be somewhat inflated by inappropriate, excessive, and/or erroneous charges. Much of the difference between the amount billed and the amount paid was borne by the provider, the patient, the insurance companies, Medicaid, and/or other government (city and county) entities. The true cost was felt to lie somewhere between the amount paid and the amount billed, but was thought to be closer to the amount billed.

There were 464,947 paid claims for services identified with one of the eleven targeted diseases during the study period. These claims represented 0.83% of the 56,346,515 Medicaid paid claims during that period.

We then compared the dollar amounts billed and paid during the study period. \$115.6 million were billed and \$66.1 million were paid on behalf of claimants with one or more of these 11 disorders. Payments for identified claimants with one or more of these targeted disorders represented 4.68% of the \$1.36 billion paid for all Medicaid services in the study period.

We examined payments by billing type: 38.37% of payments were for inpatient services and 49.7% were for long-term care services, for a total of 88.07% for these two types of services; 8.18% was for outpatient services; and 3.75% for other services.

When we looked at Medicaid payments by disease, congenital heart disease accounted for 49.2% of the \$66.1 million, with \$32.6 million spent for the care of claimants with this disorder. Down syndrome was second at \$22.8 million (34.5%).

The other disorders, in order, were: spina bifida, \$4.1 million (6.2%); sickle cell disease, \$3.2 million (4.8%); cystic fibrosis, \$2.2 million (3.2%); muscular dystrophy, \$1.6 million (2.4%); cleft palate, \$1.5 million (2.3%); neurofibromatosis, \$0.9 million (1.4%); hemophilia, \$0.9 million (1.3%); thalassemia/Cooley's anemia, \$0.4 million (0.6%); and phenylketonuria, \$0.4 million (0.6%). If one totals these Medicaid payments, they amount to \$70.5 million; but this total represented \$4.4 million of duplicated dollars, i.e., the same dollars were identified with more than one disease because a subgroup of patients had more than one disorder (e.g., Down syndrome and congenital heart disease). The unduplicated total was \$66.1 million for these 11 disorders during the nine-month study period.

We examined diseases by the types of services they required. Those diseases with more than half of billed dollars attributed to inpatient services were sickle cell disease (75.8%), cystic fibrosis (66.7%), congenital heart defects (66.7%), spina bifida (65.4%), thalassemia/Cooley anemia (61.9%), cleft palate (56.9%), hemophilia (53.0%), and muscular dystrophy (51.5%). Only three disorders were not represented among this group in which the majority of payments were for inpatient services. These are the top three diseases with major long-term components and include Down syndrome (81.8%), phenylketonuria (75.6%), and neurofibromatosis (40.1%). Additional disorders with major long-term care components were muscular dystrophy (35.6%) and cleft palate (32.4%). Diseases with heaviest outpatient utilization were cystic fibrosis (18.9%), thalassemia/Cooley anemia (18.2%), hemophilia (18.0%), sickle cell disease (17.4%), spina bifida (13.5%), and neurofibromatosis (11.4%). Only one disease showed heavy use of community care services and this was muscular dystrophy (15.9%).

One of our principal purposes in undertaking this study was to evaluate the relative proportion of Medicaid billings and payments for genetic services. These data are summarized in table II-1. Only four of these disorders showed billings over \$1,000: congenital heart defects; Down syndrome; spina bifida;

and cleft palate. Only the top three of these had payments exceeding \$1,000. There were no Medicaid billings or payments for two of the disorders: muscular dystrophy; and thalassemia/Cooley's anemia. The total billings for genetic services for these 11 disorders during the nine-month study period in 1987 were \$13,971, representing 0.01% of the \$115,601,150 billed for these disorders.

**Table II-1:
Medicaid Billing and Payments For
Genetic Services**

Rank Order	Disease	Billed		Paid	
		Dollars	Percent	Dollars	Percent
1	Congenital heart defects	\$ 5,489	<0.01	\$ 4,227	0.01
2	Down syndrome	4,309	0.02	2,994	0.01
3	Spina bifida	2,720	0.04	1,629	0.04
4	Cleft palate	1,115	0.04	871	0.06
5	Neurofibromatosis	790	0.05	672	0.07
6	Phenylketonuria	300	0.07	255	0.07
7	Hemophilia	275	0.02	208	0.02
8	Sickle cell disease	230	<0.01	196	<0.01
9	Cystic fibrosis	75	<0.01	43	<0.01
10	Muscular dystrophy	0	0	0	0
11	Thalassemia/ Cooley's anemia	0	0	0	0
Totals		\$ 15,303	0.01	\$ 11,095	0.02
Unduplicated Totals		13,971	0.01	10,122	0.02
Total Medicaid Dollars		\$115,601,150	100.00	\$ 66,149,499	100.00

Payments totaled \$10,122, or 0.02% of the \$66,149,499 paid for these 11 disorders during the study period. There were 11,690 claimants during the study period with one or more of these 11 disorders. Therefore, \$0.87 was paid per claimant for genetic services as compared to \$5,659 paid per claimant for all services for these 11 disorders.

As noted above, the study period for this project was nine months. Projections were made for a 12-month period. Unduplicated totals for billings were projected to be \$154.1 million or \$12,300 per claimant. Projected unduplicated payments were \$88.2 million for these disorders during a twelve-month period, or \$7,100 per claimant, per annum.

CIDC DATA

The CIDC data were examined for calendar year 1987. One characteristic of these data was that virtually all bills were paid in full because of prior authorization. Therefore, these data will not be broken down by billings and payments. When CIDC claims were considered by type of service for these 11 selected disorders, \$6.52 million (61.2%) were paid for inpatient/outpatient hospital services; \$2.03 million (19.1%) for physician/dentist/therapist services; \$1.27 million (12%) for drugs and medical supplies; \$0.76 million (7.1%) for durable medical equipment; and \$0.07 million (0.6%) for other. The total payments for all services by CIDC for these 11 disorders during 1987 were \$10.65 million.

CIDC claims, paid by disease, in 1987 were: congenital heart disease, \$5.05 million (47.5%); cystic fibrosis, \$1.97 million (18.5%); cleft palate, \$1.8 million (16.9%); spina bifida, \$1.13 million (10.6%); hemophilia, \$0.57 million (5.4%); neurofibromatosis \$80,200 (0.8%); sickle cell disease, \$44,900 (0.4%); and Down syndrome \$283 (less than 0.1%). Down syndrome was included in this list of claims paid, although it is presumed that this represents payment for an individual with Down syndrome and another primary diagnosis, presumably congenital heart disease, since Down syndrome is not a disorder covered by CIDC. Other disorders among the 11 selected for investigation, which were not covered by CIDC in 1987, included muscular dystrophy, phenylketonuria, and thalassemia/Cooley anemia.

It is noteworthy that changes have occurred in Texas CIDC coverage since 1987. There is now increased coverage for sickle cell disease beyond the bone and joint complications that were covered in 1987. In addition, phenylketonuria has been included as a disorder covered by CIDC.

SUMMARY

We estimated that the payments associated with the 11 selected diseases during 1987 in Texas included \$88.2 million from Medicaid and \$10.6 million from CIDC for a total of \$98.8 million. Patients with these diseases represented 0.83% of Medicaid claims, but 4.68% of Medicaid payments. Medicaid payments for genetic services for patients with these 11 selected disorders in Texas during a nine-month period in 1987 were \$10,122, or 0.02% of the total Medicaid payments for these claimants.

We conclude that our estimate of the Medicaid payments for these disorders in 1987 of nearly \$100 million represents a low estimate of the true medical costs for the care of these patients. This study also indicates that these 11 disorders represent a disproportionate share of Medicaid payments; i.e., these patients show a high ratio of payment per claim. We also conclude from these data that CIDC is a significant source of support for the medical care of these patients in Texas. And, finally, this study suggests that referral for genetic services represents a significant barrier for individuals in need of these services.

WORKSHOP

D. SPECIAL PROBLEMS OF RECENT IMMIGRANTS

IMMIGRATION AND THE PROVISION OF GENETIC SERVICES

ILANA MITTMAN, M.S.

THE SCOPE OF THE PROBLEM

Current data suggest that in the United States today, up to 28% of the population growth is due to immigration [1]. Immigrant populations in the United States are composed of many heterogeneous groups representing diverse ethnocultural, religious, and linguistic identities.

While some immigrants are individuals who chose, for one reason or another, to leave their country of origin and become permanent residents of another, others are individuals who flee circumstances of war, economic hardship, political persecution, and are displaced. Although safely placed, refugees, in general, are often poor, suffer from severe health problems, and show a spectrum of mental health problems similar to those experienced by veterans of the Vietnam war in response to separation, loss of loved ones, and harrowing experiences while escaping from their countries of origin. These individuals, contrary to the way they are viewed by some, come to this country because of immediate danger to themselves or their family members, and are displaced in a foreign and initially threatening environment. New immigrants and refugees entering this country face tremendous problems of adaptation that manifest themselves in many different ways. They are also faced with severe barriers limiting their access to important and essential services such as health care. We, as providers, encounter these individuals in an extremely vulnerable situation when they present for either acute or routine medical care. The hospital situation highlights problems of communication with the involvement of many professional and paraprofessional staff members who are usually uneducated with regards to the special cultural and linguistic needs of immigrant populations, who, as a whole, receive inadequate health care because

of ethnocultural, linguistic, and economic barriers. Genetic counseling services are also inaccessible to this population for the following reasons: They are largely preventive in nature, relatively new, costly with poor reimbursement, restrictive in time allowed for some interventions, and employ practices and concepts that demand both extensive educational efforts and sensitivity to ethnocultural diversity.

THE NATION'S DEMOGRAPHIC TRENDS

In April 1990, the United States Bureau of the Census will announce this decade's demographic statistics on what makes our nation what it is today. What the federal statisticians will find, according to preliminary estimates, will be one of the most far reaching demographic shifts in the 200 years of the U.S. census. The largest legal wave of immigration in 80 years, amplified by 300,000 to 500,000 undocumented arrivals annually, has added as many as 9 million newcomers to the U.S. population in the past 10 years. Just like the European immigration wave three decades ago, this recent one will have a significant mark on the nation's future. This wave has brought to this country immigrants and refugees predominantly from Asia (48% of the total immigration) and Latin America (35%), as compared to just 11% from Europe. The contribution of immigration to the total U.S. population growth accelerated from about 13% in 1960–1964 to 28% by the mid 1980s [1]. Furthermore, the number of legal immigrants rose from about 300,000 per year in the early 1960s to more than 570,000 per year in the first half of the 1980s. Some estimates suggest that the United States may now be accepting nearly twice as many immigrants and refugees as all other nations combined [2].

The U.S. Bureau of the Census has predicted that by the year 2040, the following changes will occur in the ethnic make-up of the nation: The white population will decrease to 62% from 72% currently, the black population will increase (from 12% to 15%), as will the Latino (8% to 10%) and the Asian populations (from 3% to 8%).

A. Latin Americans

According to the official U.S. census, between 1970 and 1980 there was a 61% increase in the Latino population from 9.1 to 14.6 million persons [3]. Including estimates of uncoun- ted, undocumented persons and adjusting for growth since 1980, there are probably more than 20 million Latinos, or 8% of

the total U.S. population. Demographic projections suggest that Latinos may become the largest minority group in the U.S. by the year 2000, and will reach an estimated number of almost 30 million people [4]. Although Latin Americans live in every state, 60% are concentrated in five western states: Arizona, California, Colorado, New Mexico and Texas.

B. Asian Americans

In the decade between the 1970 and the 1980 censuses, there was a 142% increase in the Asian population in the United States, from 1,538,721 to 3,726,440 individuals. According to estimates from the Population Reference Bureau, the number of Asian Americans may well exceed 10 million by the year 2000 with a growth rate of more than 7% a year [5]. The remarkable increase in Asian immigration is due to a change in U.S. immigration policy introduced in the mid-1960s. This new policy allowed for an increase in the immigration quota from Asian countries from only 5% to almost 50% of all legal immigrants in 1984.

By 1988, the total number of Southeast Asian refugees in the United States reached 882,900. About half settled in western states with 40% choosing California for residence. Texas, Colorado, and Washington each have more than 10,000 Southeast Asian refugees.

Immigrants from the Philippines and their descendants have tripled in number in the U.S. in the past 18 years and number more than 1 million people, the largest Asian-American minority in this country. Like Southeast refugees, most have chosen western states for residence.

SPECIAL NEEDS OF NEWCOMERS (AN OVERVIEW)

A. Psychological Process in Immigration

Leaving one's country of origin and resettling in a different one involves a painful process of separation from all that is familiar and loved. In the initial stages of resettlement, most new immigrants go through a process of grieving similar to that experienced after the loss of a loved one. When arriving in their new country, most immigrants encounter what is referred to as "culture shock." Attempting to adjust to a new country creates a sense of disorientation and inadequacy, and a feeling of isolation and helplessness. In this situation, the immigrant feels like he/she has regressed into childhood and can no longer

control the environment like an adult. In addition, he/she comes to the painful realization that much of their life-long experience can not be applied in their new reality!

B. Socioeconomic Status

The following socioeconomic profile exists for Latin and Asian immigrants [4,5]. 30% of Latinos are below poverty level as compared to 10.7% of Asians and 15% of Anglos; 16% of Latinos hold poorly paying jobs, compared to 15.6% of Asians and 11.6% of Anglos; and 33% of Latinos lack medical insurance including government welfare programs, compared to 11% of Anglos. It is important to note that within different populations there could be a remarkable polarity in the socioeconomic profile. For instance, while 7.5% of individuals of Pacific-Asian descent have a household income that exceeds \$50,000 a year, 24.2% live in extreme poverty.

C. Health Care Needs

There are some specific conditions that are prevalent in different immigrant groups. It should be mentioned, however, that, in general, most refugees suffer from chronic emotional and personal problems as a result of what is referred to as "Post-Traumatic Stress Syndrome." Anxiety and depression relating to this syndrome can have a delayed presentation, and occur after arrival to the resettlement location. This syndrome is experienced in response to separation, loss of family members, persecution, and witnessed atrocities in the country of origin.

The following risk factors were identified in the Latino population: hypertension, high triglycerides, lower HDL levels, and an increased risk for diabetes mellitus, obesity, and tuberculosis. The following risk factors were identified in the Asian population: an increased risk for breast cancer, a high incidence of positive PPD testing, parasites, hepatitis B antigen positive status, anemia, hemoglobinopathies, skin disorders, hearing loss, and idiopathic scoliosis.

D. Cultural Attitudes Towards Illness and Health Care In Asian Populations

In the different Pacific-Asian populations, health is perceived as the humoral balance in the body. That balance is influenced by the natural

environment, dietary habits, and the supernatural. Good health is a state of perfect harmony and balance.

Illness is perceived as an unbalanced state of body harmony. This can be caused by deficiencies or excess of spiritual, natural, physical, or social elements. Social elements include unacceptable behavior and sins performed in current or previous life. Natural elements involve heredity, pathogens, poisons, trauma, wind, and hot-cold imbalance.

Many Asians believe that the restoration of balance can occur on its own, and that events should be allowed to proceed through their natural undisturbed course. Invasive procedures therefore are not generally accepted. This particularly applies to removal of bodily fluids like blood or amniotic fluid, which are thought to have a cooling effect and, thus, weakens the body and promote illness. It is also believed that actions pleasing the gods, engaging in good deeds, or seeking the healing power of herbal medicine can restore balance.

Mien and Hmong (hill tribes from Laos) believe that sickness comes from the gods. A physician is a priest that negotiates with the gods (Shamans). Laos upperland people fear and mistrust "biomedical" practices. Western medicine is classified as "hot" and too potent. The best physician is thought to be the one that intrudes least on the body. It is important to note that Southeast Asian refugees will eventually seek Western medical practices when folk medicine does not offer immediate resolutions.

E. Cultural Attitudes Towards Health Care In Individuals of Latin Descent

In the Latin population, illness may be viewed as weakness that should not be shown to the outside. One may prefer to wait before seeking medical attention. In this population 17% of all admissions are emergency room admissions compared to 11% in Anglos.

Familisimo is an important aspect in Latin cultures. It means loyalty to extended family members and other good family friends. This extended network of support is important to recognize in genetic counseling interventions.

Male-dominant family hierarchy is another important cultural aspect to recognize. *Machismo* is the concept that the male in the family has a role as the strong protector and the person in control. Partners of patients will assume

this role and are unlikely to share their feelings even after the loss of a loved one.

The physician, *El Doctor*, is viewed as an important authority figure. However, there is an expectation of an informal friendly behavior, *personalismo*. The physician is also expected to respect the *dignidad*, the ordinary citizen. A handshake or a friendly touch is expected. The usage of "he" rather than "you" is often found offensive. This is important to recognize in working through an interpreter.

BARRIERS TO HEALTH CARE IN IMMIGRANT POPULATIONS

A. Cultural

- 1) Patient unfamiliarity with Western medical practices.
- 2) Unique cultural beliefs towards illness and health care that conflict with Western medicine practices.
 - a) Aversion to invasive procedures.
 - b) Shame in admitting the onset of illness, due to negative cultural connotations.
- 3) Provider's ignorance of the ethnocultural diversity of the patients and special needs.
- 4) Mistrust and fear (by both the provider and the patient: "uncooperative," "uncompliant" patient; "insensitive," "strange" provider).

B. Educational

- 1) Highly complex interventions, especially in regards to genetic counseling.
- 2) Unfamiliarity with procedures.
- 3) Limited availability of educational materials in appropriate literacy level and language.

C. Economic

1. Lack of health insurance due to the following:
 - a) Employment does not provide health benefits.

- b) Illegal immigrants are usually ineligible for government welfare programs.
 - c) Some individuals prefer not to apply for government welfare programs (fear they will not be able to sponsor a relative, cultural rejection of welfare, etc.).
- 2) Unfamiliarity with the American system and benefits.
 - 3) Extreme shortage of Medi-Cal/Medicaid providers.
 - 4) Lack of reimbursement by Medi-Cal/Medicaid for experimental procedures (DNA studies, "new" prenatal diagnostic measures, etc.).
 - 5) Underinsured for specialty care and preventive measures.

D. Linguistic Barriers

- 1) Monolingual or have limited knowledge of English.
- 2) Translators unavailable in most facilities.
- 3) Translators available but have inappropriate skills.
- 4) Appropriately skilled translators are available but communication is indirect, and the counseling dynamics are altered as the authority shifts from the provider to the translator.

RECOMMENDATIONS

- 1) Special programs should be available to act as a liaison between the "old" and the "new."
- 2) Bilingual and bicultural well-trained *educators* (rather than translators) to be used, preferably members of the same culture or religious group using the same language or who share the group attitudes.
- 3) Education—simple explanations accompanied by illustrations (audiovisual preferred because of low literacy skills or illiteracy).
- 4) The provider needs to acquaint him/herself with the cultural beliefs and the socioeconomic profiles of their patients.
- 5) Sensitivity and respect toward cultural beliefs of patients should be demonstrated.

- 6) Assurance of patient autonomy and informed consent. The "compliance" with procedures with which patients feel uncomfortable will bring more harm than good.
- 7) Funding for under- and/or uninsured individuals should be provided.

CONCLUSION

Providing safety and equal opportunity to those who wish to be members of free societies, or flee persecution, is what America is all about. After opening its doors, this nation is obligated to deliver equal and undiscriminating opportunity for its citizens, particularly in an issue as essential as health care. Failure to do so will not only be immoral and illegal but will also create a situation where those who are least able to cope will be afflicted with diseases and illnesses. This, in turn, will increase the nation's morbidity and mortality rate and will be costly both in human and fiscal terms. Furthermore, with restricted access to genetic counseling interventions, the indigent, as well as the newcomer groups, will be unable to exercise reproductive choice, and the nation will see an increase in the incidence of birth defects in these groups as compared to other populations.

The health care system in America today has to accept the reality of the many new Americans that have joined and will join this nation, as well as to adjust its practices to accommodate their needs.

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UNDERSTANDING THE SOUTHEAST ASIAN HEALTH CARE CONSUMER: BRIDGES AND BARRIERS

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Since 1976, over 800,000 refugees from Vietnam, Cambodia, and Laos have resettled in the United States. The first wave of refugees came in 1976–1978, immediately or shortly after the fall of their countries. The majority of the first-wave refugees were highly educated, primarily urban dwellers, had worked with Americans in their own countries, and had spent little or no time in refugee camps before the transition to the United States. First-wave refugees constitute approximately 20% of the total refugee population in the United States. The other 80% of the refugee population came into the U.S. as the second wave after 1980. The common characteristics of second-wave refugees are lower socioeconomic status, lower level of education (average four years of formal education), a rural background (primarily farmers and fishermen), and prolonged stay in the refugee camps. A majority of the second-wave refugees from Vietnam are what is known as “boat people.” They are Vietnamese who escaped Vietnam by the high seas, often raided by pirates; women and children raped; men killed; often running out of food and water; and turned away from one country after another until a safe harbor was found.

The second-wave refugees from Cambodia have suffered in other ways. They have lived through the genocide of the Pol Pot regime 1976–1978 (“the killing fields”). An estimated two to three million Cambodians out of a population of six to seven million were killed during this slaughter. Entire families were wiped out. The outside world first became aware of the atrocities committed when the second wave of Cambodian refugees began to pour over the Thai-Cambodian border in 1979. Pictures of the starving, half-dead Cambodian refugees reminded the world of images of the Biafran Famine in 1968.

A majority of the Southeast Asian refugees entered the United States with identified health problems. Common health problems among new arrivals are parasites, anemia, malnutrition, testing hepatitis B antigen positive, tuberculosis, mental health problems, growth retardation in children, and certain genetic blood disorders such as hemoglobin E, alpha-thalassemia-1, and beta-thalassemia. Several factors contribute to continued health problems:

- 1) Childbearing begins early and ends late in the reproductive years;
- 2) The fertility rate is considerably higher than the U.S. average; estimated birth rate is 28/1000 as compared to U.S. 15.5/1000;
- 3) Education level is low;
- 4) The unemployment rate is high (low economic level); and
- 5) Large family size leads to overcrowded living conditions.

The United States has one of the highest standards of health care in the world. Yet for the Southeast Asian refugees, there are many barriers to accessing this health care. In addition to those already mentioned, refugees have to deal with the barriers of:

- 1) language;
- 2) little or no knowledge of:
 - anatomy;
 - physiology;
 - germ theory and hygiene;
 - prenatal health care; or
 - family planning;
- 3) no surgical tradition;
- 4) an existing traditional healing culture;
- 5) a strong belief in curative powers of medicine;
- 6) a strong belief in fate/karma; and
- 7) health care provider insensitivity to Southeast Asian culture and beliefs.

Language is the initial barrier to health care. Vietnam, Cambodia, and Laos have not only their own national languages, but there are also many tribal languages spoken within each country. Often, the tribal language is the only language spoken by a particular tribal group. Laos, alone, has over 60 tribal groups and languages. In the U.S., there are currently over eight different languages spoken among the Southeast Asian refugees. Yet many health care providers can not tell a Vietnamese from a Cambodian, much less one tribal group from another. Asking is the best way to find out. Don't make assumptions.

While the Southeast Asian refugee's lack of understanding of human anatomy and the scientific definition of illness constitutes a major barrier to health care, the health care providers' lack of understanding of Southeast Asian concepts of health and well-being constitute an equally great, if not greater, barrier. This barrier is of significant magnitude, because the insensitivity of health care providers can immediately deter the Southeast Asian refugee from seeking health services in the future. Cultural education for health care providers is essential to overcoming this barrier.

Each of the Southeast Asian countries, and indeed each of the tribal groups, has its own unique traditional healing culture. However, due to the strong influence of Buddhism, animism, and Chinese traditional health beliefs, there is a common strain of healing beliefs and practices among the Southeast Asian refugees. The following is a synopsis of these beliefs and practices which are to be used as tool in understanding their health perceptions. They should never be used to stereotype because there are too many individual variations.

The basic understanding of Southeast Asian health culture begins with how the refugees perceive illness to originate. There are three categories of illnesses:

I. Physical, caused by:

- accidents;
- eating spoiled food; and
- some recognized diseases, such as leprosy, tuberculosis, malaria, and cholera.

II. Metaphysical (yin/yang principle) caused by:

- bad wind;
- hot/cold energy imbalance;
- incorrect diet; and
- excessive emotion

III. Supernatural, caused by:

- Soul loss; and
- Spirits

Physical causes of illness can be seen readily, such as a broken arm, a cut, and food poisoning; a direct cause and result. Some tropical diseases, such as those mentioned above, are recognized because there is medicine identified (much of it Western) that can alleviate the symptoms.

Metaphysical causes of illness are based upon the yin/yang principle. In a simplified explanation, yin/yang is the creative energy of the cosmos. It is polarity, having and showing two contrary qualities, powers, and tendencies. In terms of health, in the physical world, yin/yang operates in the functions of the human body. Psychologically, it works in the operations of the mind and its emotions. To have good health, one's yin/yang polarity must be balanced and in harmony.

STATE OF BODY BASE

cold ↔ equilibrium ↔ hot

The hot and cold classification is usually independent of such observable characteristics as form, color, texture, and physical temperature. Hot/cold is related to the quality/energy of a substance or condition. Excessive heat illnesses are generated from within the body itself. Skin eruptions, cold sores, and fevers are usually considered hot. Cold maladies are principally a phenomenon of disablement in which sensory and motor functions of the body are disrupted or entirely stopped. It is caused by intrusion of cold into any part of the body. For example, a major cause of cold illness is "bad wind," which causes a variety of symptoms from coughing to headaches, but it is primarily an intrusion of "cold" energy into the body. Incorrect diet is another cause of imbalance in the body, since most foods have innate hot and cold principles. There is a set of Southeast Asian postpartum practices and diet based upon the hot/cold balance of the body.

A major cause of supernatural illness is soul loss. (The term *soul* is used for lack of a better word.) The Southeast Asians believe that the body is inhabited by more than one soul. The numbers vary according to different ethnic groups. These souls inhabit various body parts and organs, the primary one being the head. To have good health, all the souls must be present in the body and in harmony. For a multitude of reasons, one or more of the souls can be frightened from, wonder away from, and/or lost from the body. Surgery is seen as a cause of soul loss. Soul loss can cause a wide range of symptoms from physical illness to emotional and mental problems. All the Southeast Asians have soul calling ceremonies, but perhaps the ethnic Lao have one of the most elaborate called the *baci* or *souk kwan* (calling souls). The *baci* ceremony is performed for many reasons. Illness, home coming, travelling, and occasions of

congratulations are all reasons to have a *baci*. The ethnic Lao also believe the body has more souls (36 to be exact) than the other Southeast Asians. So perhaps, it is a preventive measure to have many *bacis*. The *baci* has been successfully used in this country for psychosomatic illnesses and depression. Animism, or the belief in spirits, is strong in Southeast Asia. Illness can be caused by bad spirit or even by offending a good spirit. A person who believes his illness as caused by the supernatural will not have confidence in Western medicines and practices.

Besides the belief that the body is inhabited by a number of souls, the Southeast Asian have some other body concepts and practices that are important to know.

The head is the seat of the life essence

- highly personal and *untouchable*.
- disturbing it will cause soul loss.

Blood is the life energy force

- blood loss is irreversible.
- its use as a diagnostic measure is not well understood.

The area between waist and knee extremely private and personal

- pelvic examinations are feared.

Southeast Asians often avoid direct eye contact because

- direct eye contact is seen as flirtatious and/or aggressive.
- illness can be caused by evil eye.

Offensive behavioral gestures

- beckoning with an upturned finger (used to call animals in Southeast Asia).
- pointing (aggressive and threatening).
- slapping on the back.
- stepping over someone.
- pointing or touching with the feet (the lowest part of the body).
- stepping in front of someone.
- rising above or standing above someone.
- displaying emotions such as anger or affection.

Understanding and/or avoidance of some of these practices and concepts will greatly facilitate working Southeast Asian patients.

The Southeast Asians have many folk remedies for body pains and illnesses. As in many cultures, these remedies are primarily an oral tradition that can vary from family to family and country to country. Most of these remedies use ingredients that are available in the home, in the countryside, and/or in the local country store. Such ingredients can include tiger balm (a mentholated ointment), lime or lemon juice, salt, ginger, lemongrass, mint, onions, and garlic. Most of the home remedies are harmless and, indeed, may relieve minor discomforts. For more complicated problems, the Southeast Asian may turn to other health care sources, such as an herbalist, shaman, soul caller, Buddhist monk, pharmacists, and injectionists. While private physicians and hospitals do exist in Southeast Asia, they are located only in urban areas and are few in number. The majority of Southeast Asians will not use them, even in the urban areas. If they do use them, it is often as a last resort, and hospitals, in a self-fulfilling prophecy, come to be seen as a place to go to die. Two of the available health care sources should get special mention. The first is the pharmacist. The pharmacist can diagnose a patient by symptoms and dispense medicine as he/she sees fit. Or a patient can diagnose him or herself and order any medicine he/she desires. There is no such thing as a prescription in Southeast Asia. Even today, some of the Southeast Asians are able to obtain medication ranging from antibiotics to prescription cough medicine through the mail from Asia and/or France. While many of them underuse Western health care, they do believe in the power of medication and are familiar with certain medicines available in their countries. Injectionists are another group with whom one should be familiar—and wary. These are often former army medics or nursing aides who have learned how to give injections and set themselves up in business as injectionists, either in the cities or travelling from village to village. Again, medicine is easily obtainable and the belief in the power of medicine prevails. It is rumored, especially in California, that a few of these injectionists continue their work here in swap meets and/or flea markets.

Another home health care practice that health care providers and, indeed, school officials should be aware of, is dermabrasion. Dermabrasion is the “rubbing” or “irritation” of the skin in some form in order to relieve discomfort. It is usually done for “wind illnesses” such as muscle ache, coughing, headache, and/or sore throat. The most popular form of dermabrasion

is coining. This practice involves covering the affected area with ointment such as tiger balm, and then the edge of a coin is rubbed in a methodical manner over the area. All dermabrasion methods leave marks resembling bruises on the skin. These marks have been mistaken for child abuse. A cultural interpreter can often explain these practices before serious steps are taken, resulting in a loss of face.

Belief in karma or fate is strong throughout Southeast Asia. The majority of the people are not proactive but reactive in life. In terms of health care, taking an active role in one's own health is not fully understood. Given all the barriers keeping the Southeast Asian refugees from modern health care, health care providers must take an active role in working with these communities in order to develop cultural bridges to accessing health care.

In closing, the following is a synopsis of bridges to culturally accessing health care.

Community Outreach

- Bilingual, bicultural community worker

Linguistic Translation

- Knowledge of or trained in medical terminology in both indigenous language and English language

Cultural Interpretation

- Knowledge or training in Western/modern health practices
- Knowledge or training in indigenous traditional health concepts/beliefs and practices

Health Education

- Support of "gatekeepers" and/or community leaders
- Trained bilingual, bicultural health paraprofessionals
- Use of community bilingual media
- Development of culturally sensitive curricula
- Development of culturally sensitive and language specific materials
- Cultural sensitivity training for health professionals.

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RECENT MEXICAN IMMIGRANT WOMEN IN LOS ANGELES: IMPLICATIONS FOR HEALTH CARE INTERVENTIONS

RUTH E. ZAMBRANA, PH.D.

Mexican immigrant women who currently emigrate to the U.S. are primarily of child-bearing age. Currently, 29.2% of all live births in the state of California are to women of Hispanic origin—approximately 60% of whom are Mexican. It has been projected that by the year 2030, 48% of all births will be of Hispanic origin [1]. It is expected that a significant portion of this increase in birth rate among the Hispanic population will be related to continued immigration from Mexico to California and to the southwestern United States.

California receives a large portion of Mexican female immigrants. Although there is limited information on the reproductive health needs of Mexican immigrant women in the U.S., a few studies have begun to underscore the potential health needs of this group of women who are predominantly young and of low socioeconomic status. Cortes [2] reports that 75% of the state's undocumented workers come from Mexico. This population, which predominantly occupies low-skilled, low-paying jobs, receives less health care than other immigrant groups. They receive less health care partly because of their low income and lack of insurance benefits [3]. Additionally, they tend not to seek publicly funded services for the medically indigent, since doing so would increase the likelihood of detection and deportation [4]. In addition, they are likely to fear clinics as a result of poor services previously received [2]. The purpose of this paper is to present the preliminary findings of a study on factors which are related to initiation of prenatal care, and to identify barriers to use of prenatal care services among Mexican immigrant women.

FACTORS RELATED TO USE OF PRENATAL CARE: AN OVERVIEW

Past research has identified social risk factors which have been found to be associated with use of prenatal care among low-income and minority women. These include: low income and inadequate insurance coverage; preexisting disease conditions; poor nutrition; inadequate housing; low maternal education;

disrupted families and lack of social support; and problems of transportation and child care that impede use of prenatal care services [4]. In addition, psychosocial factors such as stressful life events, availability of social support resources, and life-style behaviors have been found to influence use of prenatal care among low-income women [5,6].

Limited empirical work has been conducted on the reproductive needs of low-income Mexican immigrant population [7,8]. In a recent study among 491 undocumented pregnant women in San Diego, access to and use of prenatal and postnatal health care services were studied [9]. The characteristics of the sample revealed that the mean amount of time in the U.S. was four years, average educational level was 5.6 years, and 63.5% were currently employed, with an average annual income of \$6,243.00. Regarding use of prenatal care, they found that undocumented mothers were three times more likely to deliver without prenatal care or with prenatal care sought late in the pregnancy. Twenty percent of the women received no prenatal care while 34.5% initiated care in the second trimester and 6.5% in the third trimester. The authors suggest that factors associated with their undocumented immigration status, such as low income, lack of medical insurance, and fear of detection, as well as lack of knowledge of availability of services, may contribute to the late initiation of prenatal care.

Bensacca [10] substantiated the finding that financial problems and refugee status were positively correlated with use of prenatal care services and unfavorable birth outcome. Work conducted in Mexico has also suggested that Mexican-origin women have limited experience with the health care system and limited information on the range of services available for diagnostic prenatal care services [11]. These studies have revealed that financial issues and immigrant status contribute to later initiation of prenatal care, which impede early detection of maternal and child health problems and the opportunity for genetic counselling.

METHODS

A sample of 66 primiparous women between the ages of 18 and 34 were interviewed at seven Los Angeles county clinics. Mexican immigrant women were defined as born in Mexico of Mexican-origin parents and residing in the U.S. for 7 or fewer years.

Face-to-face interviews were conducted by trained bilingual/bicultural interviewers. A survey questionnaire was used to obtain data on timing of

initiation of prenatal care, perceived barriers to obtaining early prenatal care, stressful life events, perceived family and friend support, whether the baby was planned, and sociodemographic descriptors which included age, type of health insurance coverage, work status, and living arrangements with baby's father.

In addition, the pregnant women were asked a series of questions regarding alcohol use, smoking behavior, and recreational drug use in the three months before pregnancy, and since they became pregnant. A scale (1 = never and 6 = daily) was used to ascertain frequency of drinking behavior, and type and frequency of recreational drugs used (marijuana, heroin, cocaine, and PCP). Information was also obtained on current cigarette smoking behavior and number of cigarettes smoked daily. In addition, data was obtained on frequency of use of prescription drugs and over-the-counter medications (OTC). These scales represent a modified version of items derived from the *Human Population Laboratory Questionnaire*.

The instrument was translated by Mexican-origin individuals. The instrument was carefully reviewed to assure compatibility with the education levels, socioeconomic status, and cultural origin (Mexico) of targeted study population. The questionnaire was also reviewed by a panel of three Mexican-origin researchers who were bilingual and bicultural. It was decided not to backtranslate the questionnaire since it was translated with particular attention to linguistic and cultural factors of Mexican-origin women within the context of the women's environment. An important methodological issue was raised during this process. The standard method, of back translation, assumes that the symbolic meaning of words is similar in two cultures. Our experiences suggest that translation needs to be conducted by a panel of experts who are sensitive and knowledgeable of language, socioeconomic status of respondents, and symbolic and cultural meanings of words within a particular social context. This area requires further exploration and elaboration in future studies [13,14].

PRELIMINARY DATA RESULTS AND DISCUSSION

Sociodemographic Profile of Respondents

The Mexican immigrant women had an average age of 21.9 years, and almost half (45.5%) were married. Their mean level of education was 8.3 years, and 55.3% were unemployed. Data on sources of income revealed that 34.8% had some form of salary, and none were receiving public government assistance,

although 27.3% received food stamps and WIC. Among the respondents, 10.8% were on MediCal, and 89.1% were self-pay, general relief, or were eligible for other types of general county assistance. With respect to planning the baby, a majority of the respondents (53.4%) reported that the baby was planned, and over 60% were living with the baby's father.

These preliminary data provided a profile of recent Mexican immigrant pregnant women who are using Los Angeles County prenatal care clinics. It reaffirms the characteristics of this population as a relatively young group of women who tend to have low levels of education and lack health insurance [15]. Education and occupational indicators revealed that almost 44% of the sample had less than eight years of schooling, and the overwhelming majority worked in unskilled or semiskilled occupations.

Use of Prenatal Care Services and Perceived Barriers

The average number of weeks at initiation of prenatal care was 14.6 weeks. With respect to trimester of initiation of prenatal care, only 50% initiated care in the first trimester, 38% in the second trimester and 12% in the last trimester. A surprising finding was that close to 80% of the respondents obtained prenatal care as soon as they wished. In regard to medical risk characteristics, 9.1% of the respondents reported that they were informed of a pregnancy-related problem, while medical records showed that 11% were identified as high risk.

An open-ended question regarding why respondents initiated care at a particular time provided interesting information on perceived barriers to prenatal care. A significant portion of the women simply did not know where to go for prenatal care. In the majority of cases, relatives such as mother-in-law and friends took or referred them to a prenatal care clinic.

Lack of money to pay for services was repeatedly mentioned by the respondents as a reason for not obtaining prenatal care. When asked about Medi-Cal, the majority indicated they were not aware of how to apply for it or felt they were not eligible. A number of respondents identified problems such as transportation, employment, and fear of hospitals or providers. For example, one respondent stated, "I was so far along, I was afraid doctors/nurses were going to scold me. Besides I had no money."

With respect to system barriers, a number of respondents indicated long waiting times for appointments, or showing up for appointments which had not

been scheduled, although they had made an appointment. Overall, the interview data revealed that these Mexican immigrant women had a general lack of knowledge of how and where to obtain prenatal care services in Los Angeles and feared the "health care system" because they did not know what to expect. These data confirm the findings of other studies which reported that immigrant women do not obtain early prenatal care due to fear of deportation or lack of knowledge on how to obtain services [9]. These latter factors may account for the relatively high percent of women, 50%, who did not initiate care until after the second trimester.

Profile of Psychosocial Attributes of Respondents

The data on life events revealed that "unusual money worries/troubles" and "change in living arrangements" were the highest ranked items. The third- and fourth-ranked order life events for Mexican immigrants were "living apart from spouse due to practical reasons," and "separated from partner or spouse because of not getting along." Close to one quarter of the sample reported that "problems with work," "fired or laid off," and "serious injury, illness, or hospitalization" had occurred since the pregnancy. The overall mean of life events was 4.1 events since the beginning of the pregnancy. In comparing our pilot data on low income Caucasian, black, and Mexican-American women, the number of life events for immigrant women was significantly higher [16].

The perceived social support data revealed that the Mexican immigrants perceived higher social support from friends than from family. This is not surprising since all respondents had been in the United States less than seven years and their families had most likely remained in Mexico. The greater reliance on friends suggests that friendship networks perhaps are more available in their communities, particularly in Los Angeles, where there is extensive residential segregation by ethnicity. However, it was noted that close to one-quarter of the sample indicated that they had no friends.

Health Behaviors and Substance Use Profile of Respondents

The data demonstrate a substantial decrease in use of all substances after pregnancy. The data on use of alcohol showed that beer was the form of alcohol most consumed (33.3%). With respect to drugs, the Mexican immigrants reported to have never used recreational drugs. Smoking patterns revealed that 70% of the respondents had never smoked, although over 25% indicated being

former smokers. For the latter category, the interviews revealed that they were very light smokers, maybe one or two cigarettes a day for a short period of time. Data on over-the-counter and prescribed medications revealed that among the respondents, over 60% used aspirin and 24% used prescribed medicines. The data show a substantial decrease in use of all substances after pregnancy.

These data on the use of drugs, alcohol and cigarettes confirm other studies which revealed that Mexican immigrant women tend to be abstainers and non-cigarette smokers (Marcus and Crane, 1985). However, Caetano (1987) has conducted studies which showed a relationship between acculturation and the use of drugs, alcohol, and cigarette smoking. Therefore, there may be differences in substance use patterns between Mexican origin women and Mexican-American women. Among this study population, the low use of any form of alcohol, drugs, and cigarettes may be a protective factor for pregnant women which may positively correlate with favorable birth outcome (Zambrana and Hernandez, 1988).

Discussion and Implications

The limited knowledge on low-income Mexican immigrant pregnant women in California and the Southwest represents a serious challenge to health providers and health care organizations. Our lack of knowledge impedes the development of appropriate and effective services to these populations. In this pilot study, only 50% of the pregnant women initiated care in the first trimester, compared to a national norm of 79% who initiate in the first trimester (Brown, 1988). Bridging the gap as reflected by the recommendations of the National Institute of Medicine and the national health goal that 90% of all women should initiate in the first trimester by the year 2000 seems distant. This has serious implications for the development of programs for genetic counselling and testing.

Mexican immigrant women represent a distinct target population within a particular context which needs to be understood. They lack knowledge about the biopsychosocial aspects of pregnancy and available services, as well as experience in using our health care system. These factors all represent major barriers to early detection and prevention of maternal and child health problems. Thus, these data point to the need to develop and validate educational materials that are culturally and linguistically appropriate for use as outreach tools among the population groups. The educational materials and messages

need to be guided by knowledge of the educational level of the respondents, and sensitivity to disclosure regarding immigrant status. The Spanish-language media, for example, radio and television, could be utilized to convey information on the importance of early prenatal care and information on genetic counseling. Furthermore, comprehensive infant assessment procedures which include newborn screening, and psychosocial and environmental risk assessment for early identification and treatment of genetic and developmental problems, should be incorporated into existing comprehensive prenatal care services for all women.

Finally, we need to conduct research on this population to better understand the context of help-seeking behaviors, lifestyle behaviors, and psychosocial stresses, which contribute to the health of mother and child. Epidemiologic research is needed to assess the extent of genetic and developmental disorders among infants and children of Mexican-origin descent, and the influence of social and environmental risk factors on these disorders. In addition, an understanding that their needs are more closely related to systemic barriers, rather than personal or cultural attributes, is critical. It is time to challenge the system which purports to serve these women, and cease to present challenges to those women who need the services.

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WORKSHOP

E. LEGISLATION UPDATE/ AUTHORIZATION AND APPROPRIATION

GENETIC SERVICES, RESEARCH, AND INSURANCE: TRACING THE LEGISLATIVE HISTORY

JO MERRILL

The purpose of this workshop is to identify the barriers which slow or halt legislative action and to recommend strategies for overcoming these barriers. To do this, we need to be familiar with legislation intended to serve people with genetic disorders. I have divided this legislation update into general areas:

- **Genetic services**, funded through the Maternal and Child Health Block Grant;
- **Research**, which includes funding for research on genetic disorders and orphan drugs, and some related issues such as fetal research and gene mapping; and
- **Insurance**, which covers many issues at the federal and state levels, including basic health insurance, risk pools, and Medicaid expansion.

GENETIC SERVICES

The National Genetic Diseases Act was enacted in 1976, and funds were first appropriated in 1978. The primary objective of the program was to deliver genetic disease information, and to provide education, testing, counseling services, and medical referral for all persons who were suspected of having or transmitting a genetic disorder. By 1981, Congress appropriated \$13 million for genetic services with grants to 38 states.

In 1981, the March of Dimes Birth Defects Foundation was urging Congress to appropriate \$20 million for genetic services so that each state would receive at least one grant. This federal funding was needed to supplement existing ge-

netic service centers and to initiate satellite clinics in an effort to expand the services to all people in each state.

I wish we could report that Congress reauthorized the program and increased the appropriation each year to keep up with new knowledge in genetics and to meet the increasing need for information and services. Unfortunately, that is not what has happened.

In 1981, at the urging of President Reagan, Congress repealed the legislation that had authorized certain health programs, including genetic, sickle cell, and hemophilia services programs. Congress created the Maternal and Child Health (MCH) Block Grant to provide funds for states to continue these programs at their discretion. However, funding for the block grant was less than the sum of previous appropriations for the categorical programs. Specifically, genetic services funding was cut by 47% to \$6.9 million.

The Department of Health and Human Services (HHS) was forced to reevaluate its program priorities. Funding for individual state genetics programs was discontinued. Now, a state must fund ongoing services from either its share of the block grant or its state appropriations.

Federal funding for genetic programs now comes from the "15% set-aside" of the block grant that is reserved by HHS. The money awarded by the genetic branch is used for regional genetics networks and other Special Projects of Regional and National Significance, the so-called SPRANS grants.

The genetic projects, funded by SPRANS grants, are crucial to serving people with unmet needs. Some of these projects include: How to serve deaf populations; how to break down ethnic and cultural barriers; and how to serve new groups such as the Southeast Asians. Unfortunately, the federal government now spends only \$7 million on these important programs.

There is good news—some members of Congress believe that genetic services deserve additional federal funding. Three years ago, a new supplemental appropriation was added to the MCH block grant for "Sickle Cell and Newborn Screening." Funding under this provision will be almost \$7 million this fiscal year. However, this was only a three-year program, and it ended September 30, 1989.

What does all this background on the MCH Block Grant mean to those at this symposium?

- 1) We need to support increased funding for the MCH Block Grant. If more money is appropriated for the MCH Block Grant, then more will

be available for genetic services. In addition, Congress will be taking a careful look at the MCH Block Grant this year. Support for genetic service programs is vital.

- 2) We need to encourage each state to use a fair portion of its health resources for genetic services. States now have discretion over the use of the funds they receive from the block grant.

RESEARCH

Adequate funding for medical research is a key legislative issue for those interested in genetic services. Elected officials need to be made aware that funding for medical research is a wise investment in America's future. The federal centers for medical research, particularly the National Institutes of Health (NIH), played a direct or indirect role in most of the medical breakthroughs our nation has experienced during the last century.

Unfortunately, federal support for medical research is being threatened. Over the past 15 years, various administrations have attempted to cut funding for medical research. This has been particularly true during the last eight years. We need to strengthen support for medical research.

Two other research issues have come up recently. First, the Orphan Drug Act was passed in 1983 and provided financial incentives to drug companies to develop drugs used to treat little-known, but serious illnesses. There is an effort underway now in Congress to increase funds to drug manufacturers from \$5 million to \$14 million. This effort needs your help.

The second issue, although controversial, is government funding in the area of fetal research. Members of Congress have asked health groups for assistance in determining the proper role for government in this issue. This is an issue that needs your input.

HEALTH INSURANCE ISSUES

Insurance is also a major issue. There is growing concern at federal and state levels about the 37 million Americans—15% of the population—who have no public coverage or private health insurance to help them pay for their medical needs.

A commission created by Congress during the enactment of the Medicare Catastrophic Coverage Act could determine the nation's health agenda for the

next decade. Formally known as the "United States Bipartisan Commission on Comprehensive Health Care"—but generally referred to as the "Pepper Commission"—the group will look at both health care and long-term care for the uninsured. The Commission is to release reports on both issues in early November.

Legislation providing basic health benefits to all Americans is pending in the House and Senate. Representative Henry A. Waxman (D-California) and Senator Edward Kennedy (D-Massachusetts) have introduced bills that would require all employers to offer health insurance. The bills also provide for assistance to people who work part-time or are not employed. The Waxman bill would require states to provide Medicaid to all uninsured persons by 1991. By prohibiting insurers from excluding coverage for preexisting conditions, the Kennedy-Waxman bills would aid seven million currently insured individuals who have health conditions that would make them uninsurable if they lost their current coverage.

In the past years, House Ways and Means Health Subcommittee Chairman Pete Stark (D-California) has introduced legislation to require all states to institute "shared-risk" pools for the "uninsurable." Representative Stark remains interested in the proposal, although it is not clear at this time if his bill will be introduced. A number of states have already enacted risk pool legislation or are considering it.

Another method of increasing access to health insurance, supported by President Bush during his campaign, is to allow individuals to "buy" Medicaid coverage. The "buy-in" proposals would allow states to offer coverage to uninsured individuals (e.g., those with preexisting conditions or those whose jobs lack benefits) on a sliding scale premium.

CONCLUSION

Elected officials have a key role to play in ensuring that genetic services are available to Americans who need them. Our job is to educate policymakers so that they understand the issues relating to genetic services, and to make them aware that individuals and organizations are concerned about genetic services.

In addition, we must educate the persons who are concerned about genetic disorders, so that they are aware of the legislative issues in this area and are prepared to be involved in the legislative process.

THE AUTHORIZATION AND APPROPRIATION PROCESS

MARY ANN WILSON

When we think of biomedical research, we think about the National Institutes of Health (NIH) located in Bethesda, Maryland near Washington, D.C. There are 14 institutes (see chapter appendix, page 179) including the National Center on Nursing. The NIH is part of the United States Public Health Service within the Department of Health and Human Services. The mandate of NIH is to conduct basic biomedical scientific research. However, NIH is responsive to the people and more attention is being given to the clinical aspect or the application of basic science.

While all of the institutes have a division of genetics, the institute totally focusing on genetics is the National Institute of General Medical Sciences. Because so many genetic conditions affect several systems of the body, the Inter-Institute Genetics Clinic was established in 1979 to bring together many areas of medicine to assist families with genetic conditions and researchers from several institutes in participating in research. The clinic makes the arrangements following referral from the family's physician.

The Department of Energy is conducting a considerable amount of genetic research. After some federal government internal debates, the Human Genome Project is being coordinated by NIH.

The Human Genome Project will map the position of each gene on each chromosome and then determine the sequence of the four-letter code of each gene. The scientists hope to discover causes of inherited diseases and produce new genetically engineered products and pharmaceuticals. The Genome Project is expected to be completed in 15 years at a projected cost of \$3 billion. The current director of the Project is Dr. James D. Watson, who co-discovered DNA, the chemical that stores genetic information. Dr. Victor McKusick is acting President of the Human Genome Organization (HUGO), which is also playing a significant role in this project.

AUTHORIZATION

Each part of the federal government has to be "authorized" to exist. This is true of the Public Health Service. The law that authorizes the Department of

Health and Human Services, the Public Health Service, and the National Institutes of Health originates in the House Energy and Commerce Committee and the Senate Labor and Human Resources Committee. The authorization bill must pass both houses of Congress and be signed by the President. This is step one for all "health-related" legislation.

APPROPRIATION

After the Human Genome Project has been authorized, the money to pay for the government agency and its operation has to be appropriated by the House Appropriations Committee where all "money bills" originate. The full House of Representatives has to pass the bill. In the meantime, the Senate Appropriations Committee writes its own money bill that has to be passed by the full Senate. Most likely, the House and the Senate bills will differ. A Joint House and Senate Conference Committee is then named to come to an agreement on the amount of money that should be appropriated—keeping in mind the agency's budget, as well as the budget framework of the entire federal government.

Step two of the legislative process that involves the appropriation of funds for biomedical research really takes place in the subcommittees of the House and Senate Appropriations Committees. In the House the 13-member Subcommittee is "Labor, Health and Human Services, Education." In the Senate, the 15-member subcommittee is "Labor, Health and Human Services, Education and Related Agencies." Generally, the full committee accepts the recommendations of the subcommittee, and the full House or Senate accepts the bill that has already passed the full committee.

The conference committee is usually composed of the ranking majority and minority members of the committees and subcommittees from the House and the Senate.

It is imperative to know the key players in the legislative process. Contact your Representative or Senators for a listing of Congressional members, committee and subcommittee members. This information also should be available in your local library and from the League of Women Voters.

The U.S. Government, through the NIH and its contract and grant award peer-review system, funds more biomedical research than any other country in the world or any other entity in the United States (see table II-2).

Ranked second to NIH in the amount of money spent on genetic research in this country is the Howard Hughes Institute, which is also headquartered in

Bethesda, Maryland. The Hughes Institute is one of the prime movers in the Human Genome Project Legislative Update.

**Table II-2:
Support for Health-Related Research and Development
In the United States, by Source***

Source	Amount Spent (millions of dollars)		
	FY 1986 (actual)	FY 1987 (estimated)	FY 1988 (projected)
Government	7,916	8,983	9,643
Federal	6,895	7,839	8,447
[NIH]	[5,005]	[5,851]	[6,319]
State and local	1,021	1,143	1,197
Industry	5,915	6,928	7,740
Private, nonprofit	714	739	747
Foundations	083	126	108
Voluntary health agencies	232	256	282
Howard Hughes Medical Institute	247	183	179
Other	152	174	179
Total	14,545	16,649	18,130

*Source: Report of the National Commission on Orphan Diseases: February, 1989

ISSUES IN GENETIC RESEARCH

Be alert to the many issues involved with genetic research that can affect our global society. Watch for reports of the rapid developments in genetic research and public policy in the newspapers and on the news. Some of the issues are listed below:

- Funding of genetic research and genetic services
- Human Genome Project 1989–2004 (15 years)
- Confidentiality for research participants

- Consumer and health care providers' perspectives reflected in public policy
- Genetic testing
- Voluntary versus mandatory
- Ethics
- Confidentiality
- Discrimination in insurance and employment
- Fetal research

(Currently a moratorium is in effect on all fetal research being conducted using federal funding. This is an example of a response to direct political pressure.)

- Animal research
- Participation in biomedical research
- Guidelines
- Ethics
- Donating tissue/body for research
- Cost for the participant
- Commercialization of tissue and body fluids (i.e., marketing your blood).

VOLUNTARY ORGANIZATIONS

The Alliance of Genetic Support Groups is a coalition of organizations representing people affected by genetic disorders. The alliance is dedicated to fostering a partnership among consumers and professionals in order to enhance education and service, and represent the needs of families and individuals affected by genetic disorders. The activities of the coalition increase awareness about genetic conditions, improve the availability and appropriateness of genetic services, and represent the common needs and concerns of its constituency on the national and international scene.

The National Organization for Rare Disorders (NORD) is a coalition of organizations representing diseases with an incidence of 200,000 or less in the United States. Most of the conditions are genetic. The organization is an outgrowth of the voluntary disease organizations' successful lobbying campaign

for the passage of the Orphan Drug Act in 1983. The Orphan Drug Act provides a tax incentive for pharmaceutical companies to develop drugs for conditions of low incidence that would not bring a profit.

In early 1989, the National Commission on Rare Disorders presented its report to Congress. The report states the needs of patients, physicians, researchers, the pharmaceutical industry, voluntary organizations, private foundations, and the federal agencies associated with all rare diseases. The report also makes recommendations for each of those components. A copy of the executive summary of the commission report or the full report may be obtained from your Representative or Senators in the U.S. Congress.

The role of voluntary organizations is crucial in the legislative process. Many of the NIH and Food and Drug Administration (FDA) research grants get approved through the peer-review process (i.e., authorized), but do not get funded (i.e., money appropriated). The voluntary organizations provide the expertise on their particular condition and the coalitions pool that knowledge to show how extensive their needs really are. The groups are also able to provide contacts from all over the country who can explain to the legislators what it is like to live with a genetic condition 24 hours a day, what is involved with the health care, and what can be done to help.

Without the individuals affected by genetic disorders and their active participation in biomedical research and the legislative process, nothing would get done. A comment made by Jane Lin-Fu, M.D., Chief, Genetics Services Branch of the Office of Maternal and Child Health, at this symposium provides some food for thought. She said that if there is not public involvement in developing public policy, then those with genetic diseases may be "over served" because they did not give input as to their real needs. They will be given what somebody else thinks they need.

We must accept the challenge as individuals, voluntary organizations, and coalitions to become knowledgeable in the issues that affect biomedical research, health care, genetic services, and the legislative process. We must resolve to translate that knowledge into action that will enable the families affected by genetic disorders to be better served.

CONGRESSIONAL AGENDA

DESIREE DODSON

There is an increasing concern about the 23 million workers, or dependents of workers, and the 12 million children who have no public or private health insurance to protect them against spiralling medical care and catastrophic health costs.

The growth of the uninsured or inadequately insured population has occurred at a time when changes in the reimbursement policies of insurers has created a national crisis. Individuals with genetic disorders have needs that are generally predictable and require greater amounts of health care. Their lack of adequate health care coverage and ensuing financial distress has led Congress to focus on the following issues:

- Access to health coverage regardless of preexisting conditions;
- Adequacy of health insurance;
- Affordability of insurance in relation to needs; and
- Availability of health care providers who can deliver adequate services

Clearly, it will take strong leadership from Congress to resolve this critical care issue for the nation.

One new development that highlights the increased focus on access to health care insurance is the expansion of the Senate Finance Subcommittee on Health. There are now two subcommittees: Don Riegle (D-MI) chairs the Subcommittee on Families and the Uninsured, while Jay Rockefeller (D-WV) heads the subcommittee on Medicare and Long-Term Care.

There are a number of groups looking at the problem of the uninsured and proposing solutions. A recent (January 30, 1989) report of the National Leadership Commission on Health Care, chaired by former Congressman Paul Rogers, recommended a system to supplement our current, employment-based system of health insurance coverage. The Rogers Commission recommended that individuals lacking insurance be able to purchase it through a public pool funded by premiums paid by employers and all individuals with incomes over 150% of poverty. Individuals living in poverty would have insurance purchased for them.

Legislation for health care financing will change as the groundswell of support for consumers increases. For example, individual states have begun to rise to the crisis of discriminatory health insurance practices.

A front runner in this endeavor is Arizona, which enacted a law to protect citizens from unfair discrimination on the basis of a genetic condition, developmental delay, or developmental disability.

House Bill 2517 includes the following section:

The rejection of an application or the determining of rates, terms, or conditions of a life or disability insurance contract on the basis of a genetic condition, developmental delay, or developmental disability constitutes unfair discrimination unless the applicants' medical condition and history, and either claims experience or actuarial projections establish that substantial differences in claims are likely to result from the genetic condition, developmental delay or developmental disability.

It is the role of the consumer to continue to appraise governmental servants of the financial devastation created by the escalation of medical cost and the exponential decrease in the ability to be adequately insured.

A PARENT'S PERSPECTIVE ON CREATING CHANGE IN LEGISLATION

ROBERTA M. SICH, M.A., L.S.P.

A parent can feel overwhelmed at the thought of creating change within government agencies or the legislature. It is next to impossible to be an effective voice of one. However, armed with the facts, figures, and support of a coalition, a parent's feeling of being overwhelmed can be reduced significantly. Parents and professionals can join together to create a strong voice on behalf of individuals born with genetic defects. As a parent who has worked with coalitions, I would like to share my thoughts and experiences with you.

I am the parent of a daughter born with spina bifida. My husband and I joined our local parent support group to learn more about our daughter's birth defect. Through the years, we have become active participants in a state coalition of spina bifida parent support groups, the Ohio Spina Bifida Coalition (OSBC). The purpose of the coalition as stated in the bylaws is:

To foster and promote the human rights and well-being of all persons having the condition known as Spina Bifida.

This organization has worked on legislative issues affecting individuals with spina bifida. OSBC currently is addressing legislative concerns in education, service eligibility, and medical needs of children and adults born with spina bifida. The coalition has sought other state support systems to assist them with these endeavors. By seeking the help of other organizations with similar goals, OSBC becomes a stronger voice that is heard by state department officials and lawmakers. Let me elaborate on the networking that the Ohio Spina Bifida Coalition has developed. OSBC spends minimal time, energy, belongs to three coalitions, and uses the assistance of the Ohio Legal Rights Service.

Ohio Legal Rights Service (OLRS) is an organization established in Ohio to protect and advocate for all citizens with disabilities. OLRS can give legal guidance in interpretation of laws affecting the disabled, as well as assist individuals who feel that their rights have been violated because of their disability. The organization provides assistance to OSBC by presenting workshops, addressing protection and advocacy concerns, and publishing literature that educates members of OSBC about rights for the disabled. OSBC spends minimal time, energy, and funding to address legal issues because of the services offered by this agency.

Many new bills are introduced to Ohio's lawmakers during each legislative session. It is impossible for one individual or group to track each piece of legislation as it proceeds through Ohio's system and evaluate its effect on individuals with developmental disabilities. As a result of the need to track and evaluate legislation, the Mental Retardation/Developmental Disabilities (MR/DD) Legislative Coalition was formed to oversee the legislative endeavors in our state. This coalition's stated purpose is ". . .to provide a forum for groups to identify, discuss and work toward the common goal of providing services for individuals with developmental disabilities."

The MRDD Legislative Coalition is concerned at present with five major issues in Ohio: adult services, early education and intervention, family resources, residential services, and school-age programs. This coalition tracks legislation as it develops in these areas, as well as bills of interest to the coalition's members. The MR/DD Legislative Coalition provides analysis of bills, schedules of legislative hearings, and testimony before legislators. OSBC is a member of this coalition and benefits from all of these services. The information received from the MR/DD Legislative Coalition is invaluable in keeping OSBC informed of the current bills before Ohio's lawmakers.

To address the specific needs of education for our children, OSBC has become a member of the Ohio Coalition for the Education of Handicapped Children (OCEHC), which focuses its activities exclusively on the education of handicapped children in Ohio. This coalition is committed to insuring that the right to an appropriate education for every handicapped child be no less than that of a nonhandicapped individual in the state of Ohio. OCEHC has many programs that address the overall educational needs of children with disabilities. One vital program is closely monitoring bills that affect education and state departments providing for the educational needs of children with disabilities. OCEHC provides analysis of current bills affecting the education system and direct testimony to legislators on behalf of all of its member organizations. OCEHC also publishes information that assists individual member organizations in advocating for legislative issues not addressed by the coalition.

A third coalition in OSBC's network is the Ohio Developmental Disabilities Alliance for Service Eligibility (ODDASE). ODDASE was established to analyze the current service delivery model for individuals with developmental disabilities in Ohio, and to work to modify the current Ohio definition of developmental disabilities to a functional definition. ODDASE legislative efforts focus on one issue—changing the definition of developmental disability in Ohio.

BARRIERS THAT SLOW OR HALT LEGISLATIVE ACTIONS

This system of coalitions is not without problems. A single organization, such as the Ohio Spina Bifida Coalition, may find that its focus is somewhat diluted by this networking. Coalitions may not always address the individual member's specific concerns. In deciding to join, the prospective member should determine if the coalition has a broad or narrow focus on legislative issues. If

the coalition addresses a narrow topic, then can the concerns of individual members be addressed? A strong voice is important for every member of a coalition. Can the new member afford the time commitment needed to meet the requests of other coalition members? There may be an immediate influx of requests from members that cannot be ignored. This can be frustrating and ineffective if not enough information is provided to respond intelligently. An individual member must be willing to study issues of other members of the coalition to effectively address the varied needs of each group.

There will be letters to write, meetings to attend, and phone calls to make. A time commitment is required in order to learn how to testify effectively and be willing to provide testimony on short notice. Coalition membership can be costly in terms of both time and money, and prospective members must determine their level of participation. It is not an easy task for parents to make such time and monetary commitments for coalitions. However, the commitment must be made. Society does not change its attitudes about the disabled without determined parents and supporters who are willing to unite and give of themselves to develop appropriate laws for citizens with disabilities.

Parents must also have patience in understanding that it takes time to effect a major change in legislation. A bill begins in a study committee before it ever reaches a subcommittee of one of the legislative bodies. Testimony must be provided to the study committee, then the subcommittee, and perhaps the full committee, as a bill makes its way to a final vote. Letter writing campaigns will be needed, along with phone calls, and meetings with local legislators in their home offices to educate them about the specific issues surrounding a bill. Still, the bill may die at any step in the legislative process during a session, only to have to be introduced in the following session.

METHODS BY WHICH LEGISLATORS AND THE PUBLIC CAN BE EDUCATED

Despite the barriers I have just mentioned, coalitions are effective. They are an excellent means of keeping abreast of legislation and showing lawmakers the large numbers of unified constituents who are interested in laws for the disabled. A coalition can provide a voice for one person to be heard in an effective manner.

There must be a constant flow of public awareness activities on developmental disabilities and issues affecting this population at the local, state, and

national levels. With a little time and effort, parents and local support groups can provide information to the general public and legislators in any number of ways. These might include distributing educational pamphlets, providing a phone number that can be used to give information about a specific disability, creating a slide presentation or a speakers' bureau for local community organizations or schools to use, or providing interviews and pictures for newspaper articles or local television spots. Public awareness should be a consistent and top priority for any parent support group if that group expects to receive support from the general community.

In the state of Ohio, an organization has been formed to assist parent support groups with their public awareness activities. It is an impressive organization that has become effective not only as a support system, but in providing public awareness activities in its own right. This organization is called Ohio Public Images (OPI). It provides public awareness tools and techniques to advocates, parents, service providers, and to individuals with developmental disabilities. Major activities of OPI have included: "And Justice for All," an awareness program for Ohio law officers about individuals with developmental disabilities; "1701 James Street," a black-and-white photo exhibit/documentary about group homes for the mentally retarded; "The PR Puzzle . . . Where Do You Fit In?" a program for parent support groups to establish and maintain a communications program with the media; "Building Understanding Through Language," an article printed in a publication reaching the 11,000 members of Women in Communications, Inc.; and "Partners for Community Living Awareness Curriculum," developed to promote awareness of individuals with developmental disabilities to middle and junior high school students. OPI also has established an annual awards banquet recognizing local media for presentations that have promote awareness an understanding of people with disabilities.

Finally, there is need for a personal commitment to educate those with whom we come into daily contact. No opportunity to educate the public should be ignored. It is surprising how little others know about disabilities and problems of the disabled. Speaking with individuals, answering questions about disabilities, and providing written material to others is a very personal, effective way in which to provide public education. Parents must be aware that there will always be a need to educate those around them about their child's disability if they want their child to be treated with respect and dignity. No one knows more about a child's disability, and how that disability affects their

child's personal needs, than parents who provide daily care. If parents assume others know about their child's disability, they are taking a naive risk for their child's future independence and rights.

Parents can be effective by providing any level of commitment. Not everyone has the stamina, time, and resources to work toward changing legislation for individuals with developmental disabilities. However, all can be committed to doing their parts when asked. And everyone should remember that change will not occur without education—even education of friends and neighbors. For parents of children born with genetic birth defects, part of helping their child must be educating those whose lives they touch. It is the responsibility of the professionals who serve these families to provide parents with the knowledge and encouragement to educate others for the sake of their child with a developmental disability.

CHAPTER APPENDIX

THE NATIONAL INSTITUTES OF HEALTH BETHESDA, MARYLAND

National Institutes of Health
(Vacant)
Building #1, Room 124
Bethesda, Maryland 20892

National Institute of Child Health and
Human Development
Duane F. Alexander, M.D., Director
NIH Bldg. #31, Room 2A03
Bethesda, Maryland 20892

National Cancer Institute
Samuel Broder, M.D., Director
NIH Bldg. #31, Room 3A52
Bethesda, Maryland 20892

National Institute of Neurological
Disorders and Stroke
Murray Goldstein, D.O., M.P.H.
NIH Bldg. #31, Room 8A52
Bethesda, Maryland 20892

National Institute of General Medical
Sciences
Ruth Kirschstein, M.D., Director
NIH Bldg. #31, Room 4A52
Bethesda, Maryland 20892

National Eye Institute
Carl Kupfer, M.D., Director
NIH Bldg. #31, 6A03
Bethesda, Maryland 20892

National Institute of Dental Research
Harald Loe, M.D., Director
NIH Bldg. #31, Room 2C39
Bethesda, Maryland 20892

National Center for Nursing Research
Doris Merritt, M.D., Director
NIH Bldg. #38-A, Room B2E17
Bethesda, Maryland 20892

National Institute of Arthritis,
Muscular and Skin Diseases
Lawrence E. Shulman, M.D.,
Director
NIH Bldg. #31, Room 9A35
Bethesda, Maryland 20892

National Institute of Heart, Blood and
Lung
Claude L'Enfant, M.D., Director
NIH Bldg. #31, Room 5A52
Bethesda, Maryland 20892

CHAPTER APPENDIX

THE NATIONAL INSTITUTES OF HEALTH BETHESDA, MARYLAND (CONT'D)

National Institute of Aging
T. Franklin Williams, M.D., Director
NIH Bldg. #31, Room 5A35
Bethesda, Maryland 20892

National Institute of Allergy and
Infectious Diseases
Anthony S. Fauci, M.D., Director
NIH Bldg. #31, Room 7A03
Bethesda, Maryland 20892

National Institute of Diabetes,
Digestive and Kidney Diseases
Philip Gorden, M.D., Director
NIH Bldg. #31, Room 9A52
Bethesda, Maryland 20892

National Institute on Deafness and Other
Communicative Disorders
Jay Moskowitz, Ph.D., Acting Director
Shannon Bldg., Room 103
Bethesda, Maryland 20892

Inter-Institute Genetics Clinic
Sandra Schlesinger, M.S., Coordinator
NIH Bldg. #10, Room 9C436
Bethesda, Maryland 20892
(301) 496-1380



Theme **III** Strategies
& Model
Programs

PLENARY ADDRESSES

THE FEDERAL OFFICE OF MATERNAL AND CHILD HEALTH'S ROLE

JANE S. LIN-FU, M.D.

I am pleased to present a brief overview on the efforts by the Office of Maternal and Child Health (OMCH) in improving genetic services for underserved populations. The OMCH is the major federal contact point in the U.S. Public Health Service of the Department of Health and Human Services for state and local governments, as well as voluntary organizations concerned with maternal and child health. It is responsible for administering the MCH Block Grant Program to improve the health of mothers and children, including children with special health care needs. The OMCH also supports many Special Projects of Regional and National Significance, or SPRANS, through the 15% set-aside funds from the MCH Block Grants appropriation earmarked for this purpose. These special projects, or SPRANS, include training, research, genetics, hemophilia and other projects to improve the health of mothers and children. The genetics SPRANS include over 50 projects related to genetic screening, education, counseling, and other services. These are administered by the Genetic Services Branch (GSB) of OMCH.

Among the projects funded by the GSB are the ten regional genetics networks and the Council of Regional Networks (CORN) for Genetic Services. The networks are comprised of state representatives in a geographic region who are concerned with the delivery of genetic services. Their major objectives are improvement of communication, sharing and coordination of resources, data collection, education, quality assurance of laboratory services, and examination of reimbursement issues related to genetic services. This national symposium grew out of the effort of one of the networks, the Mid-Atlantic Regional Human Genetics Network or MARHGN. The OMCH, through MARHGN, has provided funding for this symposium, and has also participated in its planning.

The CORN is the national coordinating body for the regional networks and serves as a forum for ideas and plans in genetic services that have emerged from regional activities. It is comprised of delegates from each regional genetics network.

First through MARHGN and now through CORN, OMCH has supported the Alliance of Genetic Support Groups, which is dedicated to fostering a partnership between consumers and professionals to enhance education and service for, and represent the needs of, families and individuals affected by genetic disorders.

The activities of CORN, the regional genetics networks, and the Alliance contribute significantly to the improvement of access to genetic services, particularly for the underserved.

In addition to supporting CORN and the networks, OMCH also supports several demonstration projects that focus on the provision of genetic services for the underserved.

Racial and ethnic minorities, who are largely underserved not only by genetic services but also by other health services, have received special attention. Sickle cell anemia, which affects largely, though not exclusively, the black population, is a major concern to OMCH. The OMCH co-sponsored and actively participated in the planning of the 1987 National Institutes of Health Consensus Development Conference on Newborn Screening for Sickle Cell and Other Hemoglobinopathies. Before the FY 1987 Supplemental Appropriation Acts (P.L. 100-71) provided special funds earmarked for newborn screening for sickle cell and other genetic disorders, the Genetic Services Branch of OMCH supported with its regular budget four states (Georgia, North Carolina, South Carolina and Tennessee) to initiate statewide newborn sickle cell screening in FY 1986, and funded three additional states (Louisiana, Mississippi, and New York) in FY 1988. After the special supplement became available, late in FY 1988, five more such projects were funded (California, Florida, Illinois, Virginia, and South Carolina) and 11 states (Alabama, Arkansas, Connecticut, Iowa, Kentucky, Maryland, Massachusetts, Missouri, New Jersey, Rhode Island, and Texas) and the District of Columbia were funded in FY 1989. A project at Emory University to provide technical assistance to states in

initiating newborn sickle cell screening has been supported by OMCH since FY 1986.

The OMCH is also supporting a research project at Baylor University to demonstrate the practical applicability of DNA technology for confirmatory diagnosis in newborn screening programs for sickle cell anemia. In FY 1989 a total of \$715,647 were spent from the GSB's regular budget and an additional \$3,885,600 from the special supplement to support newborn sickle cell screening. In FY 1990, we anticipate to obligate over \$6 million for this purpose.

It is important to note that this is the last fiscal year of the special supplement. The funds earmarked for newborn screening for sickle cell and other genetic disorders is expected to sunset and be returned to the MCH Block Grant next year.

Aside from this important undertaking in newborn screening for sickle cell anemia, the OMCH has also supported several demonstration projects to provide outreach genetic services for the underserved minorities, including blacks, Native Americans, Hispanics, Southeast Asians, and Haitians. Overcoming ethnocultural barriers to genetic services was an area of priority for funding in FY 1989 and will be again in FY 1990. In the past, ethnocultural barriers have been perceived by many as a one-sided problem. Many health professionals erroneously thought that it is only the service consumers who have the barriers because they fail to understand the health care system, do not comprehend the causes of diseases and proper treatment, or do not speak English. We, at GSB, feel that it is critical to educate the health professionals to recognize their role in cultural barriers, to be culturally sensitive, and to provide culturally appropriate services. To overcome ethnocultural barriers to genetic services, education must be directed at both the health care providers and service consumers. One can expect poor service utilization, poor patient compliance, even patient alienation, and ultimately a waste of health resources if the services offered are not culturally sensitive and appropriate.

In FY 1989, nine projects with a total funding of \$1,304,077 were devoted to outreach efforts and overcoming ethnocultural barriers to genetic services. In addition, two projects were funded to increase access to genetic and other MCH services among Southeast Asian refugees because this minority is a rela-

tively new but rapidly expanding population whose genetic problems have received only limited attention so far.

The hearing impaired are another underserved population that have received only limited attention. Two of our projects, one at Gallaudet Research Institute in Washington, D.C., and the other at St. Christopher's Hospital for Children in Philadelphia, are targeted at the hearing impaired.

The budget of the GSB is very limited, but aside from direct funding of demonstration projects such as those mentioned above, we hope that through activities of CORN, the regional genetics networks and Alliance, and symposia such as this, the impact of the limited dollars on improving services for the underserved will be multiplied by those committed to bring true equality in genetic services to all.

GENETIC SERVICES: THE MARCH OF DIMES' ROLE

BEVERLY RAFF, PH.D.

Genetic services are increasingly recognized as a valuable component of obstetric, pediatric, and adult medicine. However, barriers to care deny many people the opportunity to benefit from these services. Obstacles include geographic isolation, financial restraints, cultural and language differences, social stigma, and gaps in professional knowledge and public awareness as the interdisciplinary field of genetics rapidly changes.

The March of Dimes has employed a variety of strategies to help overcome these barriers. This presentation will highlight a few of the efforts of the foundation and its volunteers in the field of genetics.

For many decades, the March of Dimes has been an integral part of research advances that laid the groundwork for today's clinical genetic services. The

record of achievement goes as far back as the discovery of the double helix structure of the DNA molecule. James Watson was supported by a March of Dimes fellowship when he collaborated on this Nobel Prize-winning feat in 1953.

Research is important, and the March of Dimes devotes a substantial portion of its research budget to genetics. But victories in the research laboratory can only save lives when support is available to translate them into practice, so that treatment and prevention exist. The March of Dimes assists in bridging the financially precarious, time-consuming gap between research success and effective, accessible, and acceptable medical service.

One recent example: In 1983, Dr. Barry Wolf, at the Medical College of Virginia, discovered that the inherited lack of a vitamin-B recycling enzyme, biotinidase, was the cause of a serious, sometimes fatal, cluster of neurological problems in children who had appeared normal at birth. With support from the March of Dimes, Dr. Wolf supplied the link between research and prevention, devising an inexpensive and reliable test to screen newborn babies for the deficiency. A statewide pilot screening program proved the test's accuracy and value; adding biotinidase-deficiency screening to other newborn screening tests costs less than 25 cents per baby. Early detection and prompt treatment with vitamin supplements prevent the mental retardation, seizures, and deaths that accompany this easily treated inherited disorder.

After the March of Dimes demonstrated the value of the test, it was time for the state of Virginia to take over. In 1986, it passed a law making the test mandatory. Now more than a dozen other states and countries are establishing their own detection and prevention programs.

As new DNA-based diagnostic techniques are developed through research, March of Dimes medical services programs are helping make them available and affordable for people around the country. Currently, we support three DNA-based diagnostic programs. Two (in Rochester, Minnesota, and Memphis, Tennessee) offer carrier testing for the female relatives of males with hemophilia, regardless of ability to pay. The second program (in San Francisco, California) provides DNA-based diagnosis for sickle cell disease.

From the beginning, March of Dimes genetic services have been guided by the same principles that led us to support Dr. Wolf's work—taking a chance on in-

novative ideas, demonstrating effective service models, and providing the seed money to make services accessible until long-term funding sources are identified.

Through our public affairs division, we work to ensure that funding. The March of Dimes was active in advocating for extension and funding of the National Genetic Diseases Act. March of Dimes chapters encouraged increased funding for newborn screening and other genetic services within the Maternal and Child Health Block Grants.

In the 1970s, the March of Dimes put genetic services into place throughout the country, expanding the number of centers from 10 to more than 100. From 1970 until 1978, the March of Dimes was *the* major funder of genetic services in the nation—larger than the federal government or any other agency. Grants were administered under a five-year “seed money” policy that provided screening, laboratory equipment and testing, counseling, and prenatal diagnosis. The model we created for genetic service centers was designed for outreach: Each specialized center conducted satellite clinics to bring services to people in geographically isolated areas. The federal government followed the March of Dimes prototype after it took over as the major funder for genetic services.

When professionals went into local communities from March of Dimes genetic centers, physicians and other primary care providers were encouraged to accompany their patients to the visits—thereby educating and planting the seeds of genetic awareness in the minds of local practitioners. March of Dimes professional education continues at many levels. One audiotape sensitizes physicians to the concerns of families with genetic disorders. This tape was a by-product of the first conference (“Genetic Support Groups: Volunteers and Professionals as Partners,” June 1985, Washington, D.C.) that addressed the issues facing individual families who must cope with genetic disease. It was at this conference that the idea of an alliance for genetic support groups was first developed.

At the national and international level, we support an annual clinical genetics conference to bring together basic scientists and clinicians, the Bar Harbor short course in genetics, and periodic international meetings on cytogenetic nomenclature.

Since the early days of the organization, the March of Dimes has realized that providing services is not as straightforward as merely writing a check to pay the bills. To produce quality services for complex problems, inventive education and career development is often required. In the days of polio, it meant supporting major curriculum changes and training in the field of physical therapy—actually doubling the number of physical therapists in the country to meet the crisis. In genetics, it has involved creation of an entirely new health professional—the genetic counselor.

This year we congratulate the National Society of Genetic Counselors on their tenth anniversary. For the last 20 years, the March of Dimes has believed in and supported the development of this profession by working in curriculum development, providing financial assistance to trainees, demonstrating the vital service role that these professionals could play, supporting the formation of the counselors' professional association, and, in 1980, commissioning the largest and most comprehensive evaluation of genetic counseling ever conducted.

The work of genetic counselors, nurses, and social workers is particularly vital in expanding genetic services into underserved communities. One highly successful program began at Georgetown Hospital in the District of Columbia. The District has several hospitals offering excellent genetic services. However, thousands of residents receive most of their medical care in neighborhood maternal and child health clinics, where nurses and social workers know the families best.

During the last seven years, more than 300 clinic nurses and social workers in the Baltimore/Washington area have been trained in March of Dimes-sponsored, five-month courses. They learned to identify families who might benefit from genetic services, to make referrals, and to provide community-based follow-up care. Sessions for the health professionals to learn from consumers were integrated into every course—and, in fact, were consistently rated by students as the most beneficial aspect of the course. This year, the Georgetown program is being expanded nationwide, with a five-day preceptorship to train 20 nurses, social workers, and psychologists sponsored by their local March of Dimes chapters.

In different projects throughout the country, the March of Dimes is trying to bridge linguistic and cultural barriers that may prevent communities from receiving the services they deserve. Most March of Dimes educational materials are available in Spanish and English. In Seattle, bilingual Asian women from several new immigrant communities have been trained to provide culturally relevant educational materials and to aid communication between pregnant Asian women and their Western health care providers. In Los Angeles, written materials on thalassemia screening, maternal serum alpha-fetoprotein (MSAFP) screening, genetic counseling, and the prevention of birth defects have been translated into Vietnamese, Cambodian, Lao, and Hmong.

The March of Dimes also believes that successful genetic services must be offered within the context of family values. Our emphasis on sensitive and skilled counseling starts from a simple premise: The diagnosis of a genetic disease is a crisis. And, at a family level, when there is a crisis or a difficult decision to make, people often turn to the clergy for advice and support. By 1980, families were approaching their ministers, priests, and rabbis with many questions that were outside the experience of most clergy—questions involving new information about inherited disorders, and unprecedented and complex new options in decision making about childbearing. In an attempt to meet the growing need for a genetically-informed clergy, the March of Dimes, in 1981, funded a national interfaith conference on "Genetic Decision-Making and Pastoral Care." With the leadership of Father Robert Baumiller, March of Dimes clergy conferences have been replicated at more than 50 sites around the country.

In recognizing and confronting barriers to comprehensive medical care, language and geographic boundaries are easy to see. But just having a chronic illness can be an isolating experience. Individually, there are thousands of genetic disorders, and hundreds of thousands of families seeking appropriate medical care, education, and adaptive services. To decrease the isolation of persons with rare disorders, and to increase their political power, the March of Dimes has supported the National Organization for Rare Disorders (NORD) and the Alliance of Genetic Support Groups. Most recently, the foundation helped NORD expand their rare disease data base, which now provides information to more than 1,300 people each month.

Some of our current research projects involve the social concerns that can isolate families living with genetic diseases. One project has evaluated educational strategies for mainstreaming children with visual impairments. Another investigator is probing the issues faced by aging parents who are the primary caregivers to their mentally retarded adult children.

And the foundation never forgets that finances are a significant part of the burden of genetic diseases, particularly in a country where the medical system is based on free market economics and an acute care model. Today, 25 million Americans are considered "underinsured;" 11 million children have no insurance whatsoever. Even families who believe they have good health insurance often receive a rude shock when it comes time to pay for all the care and treatment a genetic disorder can require.

In order to have insurance companies seriously consider providing reimbursement for genetic services, the March of Dimes funded a demonstration project with the Blue Cross/Blue Shield Association. The study's recommendations, issued in 1987, were gratifying. They recommended that their insurance carriers include coverage for several genetic services, including amniocentesis, genetic evaluation, and maternal serum alpha-fetoprotein screening. The report particularly emphasized the need for genetic counseling, stating that "covering laboratory diagnostic procedures without covering skillful interpretation for the patient and family could promote inappropriate underutilization of the counseling services."

In the 1990s, the March of Dimes will be continuing its involvement in genetic services in several key areas:

1. RESEARCH

From basic molecular questions to studies designed to answer practical questions about education and child rearing, our commitment to genetics research is ongoing. As always, the foundation's focus will be on innovation: Launching a research-minded young investigator on a career in genetics; supporting the pilot study that takes a project from good idea to readiness for large-scale investigation; translating laboratory findings into clinical tools and services.

Currently, about 10% of March of Dimes' research grant money is related to gene therapy. On its 50th anniversary in 1988, the organization announced that one of its two new initiatives would be a focused acceleration of research to develop gene therapy. A volunteer task force is helping to determine the most valuable role the foundation can play to enhance work in this area.

2. SERVICE

The March of Dimes supports demonstration projects and new service models, and continues to provide seed money to organize and introduce genetic services into underserved areas. In recognition of the limits to what a single voluntary agency can do, we will continue to be vigorous advocates for government support and insurance reimbursement for genetic services, supporting and working within coalitions to make our voices heard about the needs of people with genetic diseases and the importance of genetic services as a component in preventive care.

There are currently 133 local March of Dimes chapters, representing every community in the nation. Each chapter has a mandate to assess service needs within their community and, with local health professional advisory committees, to set priorities about ways to meet those needs. Health professionals and members of genetic support groups are encouraged to become involved in that decision-making process on a local level.

In the effort to eliminate barriers to services, local March of Dimes chapters have been asked to concentrate their efforts in one key area—helping more women gain access to early and comprehensive prenatal care. Truly comprehensive prenatal care includes access to genetic services and genetic counseling.

3. EDUCATION

The March of Dimes will continue to provide educational materials and training opportunities for professionals as well as the public. We have materials for genetic education at levels from grade school through adulthood. One of our most cost-efficient public education instruments is a group of single-page fact sheets, on more than 30 subjects, that are available for use in education and clinical work. Professional education and community services catalogs outline some of the resources available.

The March of Dimes looks forward to continued collaboration with health professionals, consumers, and government representatives as we strive to ease the burden of genetic diseases and birth defects on families.

VOLUNTARY AGENCIES

DESIREE DODSON

My own past feelings of isolation and helplessness upon receiving the diagnosis of porphyria, a rare genetic disorder, are a memorable reality to me. After my first critical attack subsided, I faced a different crisis.

First, any available literature on my disorder only confounded me to a higher degree.

Second, I was lonely for someone with whom I could communicate about my intense pain and paralyzing fears.

Fortunately, I met another porphyria patient at the same research institute. At that point, we undertook the biblical charge to bear one another's burdens, and a support system was born. In time, our group expanded as did the realization that a more formal service organization was tantamount to achieving whole health care. We learned that our self-help group enabled people to alter their condition by altering their knowledge and attitude.

Most voluntary agencies come into existence through this sequence, suggesting that additional assistance is beneficial along with traditional health care. The difficulties of individuals affected by genetic disorders and the pertinent services needed to assist them rapidly unfold to those involved in the daily activities of a voluntary group. When a person is faced with racial, financial, geographic, or disease-rarity barriers, the problems are compounded.

To address these needs and reduce the barriers for the underserved population suffering from genetic disorders, voluntary agencies have implemented a vast

spectrum of services. First, regardless of an individual's circumstances in life, people need people. Therefore, a major priority of most agencies is to link persons with similar concerns in order to provide social support through shared experiences. Also, increased knowledge in any area of life increases control over one's situation. Thus, voluntary groups develop and distribute understandable, educational materials.

Alliance is a key word in the self-help world. Unification is essential to provide substantial numbers to sway the public and legislators for improved health care for genetic disorders. For example, the National Organization for Rare Disorders (NORD) was the vital force behind the approval of the Orphan Products Board. This act provides tax incentives to pharmaceutical companies to encourage development and manufacture of treatments for rare diseases, most of which are genetic. Also, it provides funding for researchers to investigate new treatments.

At present, NORD is focusing on the major legislative changes needed in health care financing. As medical costs spiral upward, adequate health insurance has never been more unattainable for those in need.

Another coalition, the Alliance of Genetic Support Groups, provides a forum for consumer/professional collaboration to promote availability and accessibility to high quality genetic services. In November 1989, the Alliance held a national conference entitled: "Empowerment: A Symposium to Explore Empowerment Through Knowledge and Skill-Building for Individuals, Families and Professionals Involved With Genetic Disorders." One workshop focused on empowering consumers through the regional networks for genetic services. During this workshop, it became evident that consumers are not basically aware of the services of these networks.

Because the networks are already in place and are a natural link between professionals and voluntary genetic groups, the Alliance is making linkages with each network a priority. In addition, the Alliance will be establishing regional alliance groups using Alliance board members and regional genetics network leaders as resources and consultants to assure technical assistance and an information exchange. Enhancing this consumer/professional partnership is important because within the health care community there exists a lack of experience with the self-help concept and its benefits.

In contrast, many consumers consider the formal health care systems to be insensitive and unappreciative of those who have experiential knowledge of an illness, and unique perspectives to share. Thus, the Alliance is a vehicle for consumers to work more closely with professionals, and for professionals to recognize consumers as a resource in an effort to insure improved health care and greater accessibility of existing services.

Many disease-specific voluntary agencies are attempting to reduce the variety of barriers to genetic services in spite of limited funding.

- The Zain Hansen Mucopolysaccharidoses Foundation distributes financial aid and other assistance to children with this disorder. They operate a medical equipment exchange bank as well.
- The Muscular Dystrophy Association services include repair of orthopedic appliances and transportation aid.
- A treatment fund is available through the National Foundation for Ectodermal Dysplasia to assist families with the ongoing expense of dental care.
- The National Association for the Craniofacially Handicapped assists persons with severe craniofacial deformities by providing travel expenses to comprehensive medical centers.
- The American Porphyria Foundation presents quarterly teleconferences, thus enabling patients who are geographically separated from specialists to hear lectures on their disorder and participate in question-and-answer sessions.
- Most agencies work tirelessly to fund worthwhile research efforts. Additionally, some assist researchers in identifying and locating participants for their clinical research.
- Some organizations produce educational materials in several languages.
- Foremost, voluntary groups have undertaken the responsibility of enlightening the public and government bodies to the grave lapses in genetic services, especially for those facing financial devastation and inability to receive even adequate health care.

Many non-profit agencies publish legislative updates on issues, such as lack of research funding or health care financing. In fact, they have involved their members in expansive, ongoing campaigns to apprise Congress not only of the serious lack of research funding for genetic disorders, but also of the multiple barriers for services already in place. As coalitions develop, the results of these efforts will surely be more impressive than in the past.

The needs of individuals affected by genetic disorders continue to mount, and assisting with these difficulties continues to be the focal point for voluntary organizations despite inadequate funds. The success of these groups is due to the countless volunteers whose motivation is to ease the suffering of their fellow human beings.

WORKSHOP

A. OVERCOMING LANGUAGE BARRIERS

SPECIAL CONSIDERATIONS IN GENETIC COUNSELING WITH THE DEAF POPULATION

KATHLEEN SHAVER ARNOS, PH.D.

Any comprehensive discussion of language barriers that may affect genetic counseling situations must also include consideration of the deaf or hearing-impaired population. Hearing impairment is common in the United States today, with an estimated 21 million individuals having some degree of hearing impairment. The number of severely-to-profoundly deaf infants born every year in the United States has been reported to be approximately 1 in 1,000, representing between 2,000 and 4,000 infants every year [1]. It has also been established that genetic factors account for no fewer than 50% of these cases [2]. Many infants with moderate-to-profound deafness or hearing impairment learn to communicate successfully using American Sign Language or another of the sign language systems. American Sign Language (Ameslan or ASL) is, in fact, one of the more commonly used languages in this country. ASL is a distinct language with its own syntax and grammar that differ from that of English. The high incidence of genetic conditions within the deaf population is in stark contrast to other U.S. linguistic minorities, who have no greater incidence of genetic disorders than the general population.

For a variety of reasons, genetic counseling for the deaf has been limited in the past. Lack of knowledge among geneticists concerning communication methods and cultural differences have limited successful interaction with deaf persons. As with other groups, the deaf population has very little knowledge about the basic concepts of human genetics and the purpose of genetic counseling. The deaf community has traditionally perceived genetics as threatening to their cultural values. This attitude was rooted historically in the eugenics movement of the late 1800s and early 1900s; most deaf persons are aware of Alexander Graham Bell's assertions that steps were needed to discourage deaf

persons from marrying one another. Bell, a firm proponent of the eugenics movement, believed that if deaf people were discouraged from intermarriage, the number of deaf children born in this country would be greatly reduced. As he stated, this would protect against "the formation of a deaf variety of the human race" [3]. Many deaf persons associate these eugenic attitudes with modern genetics, and assume that hearing genetic counselors will try to persuade them not to have children if there is a chance that those children will be deaf. The deaf community's distrust of the genetics profession has also been perpetuated by the inadvertent use of culturally inappropriate terminology in genetic counseling and genetic education.

The Genetic Services Center (GSC) at Gallaudet University was established in 1984, through funding from a SPRANS grant from the Department of Health and Human Services, in response to the perceived need for genetic counseling services that were appropriate to the language and cultural differences of the deaf population. The GSC was set-up in a non-traditional, non-medical setting (Gallaudet University is the only liberal arts university in the world exclusively for deaf students), in order to promote access to genetic services. An indication of the accessibility of genetic services through this approach is that over 80% of the referrals to the GSC are self-referrals, in stark contrast to the situation at some other genetic centers, where the majority of referrals may come from other health care providers. Informal surveys of GSC clients and/or their parents have indicated that in most situations, genetic counseling regarding the cause of the deafness or hearing impairment was never suggested by other health care providers.

The staff members of the Genetic Services Center, including genetic counselors, a genetics nurse, and other support staff such as clerical workers and research assistants, were either fluent in sign language prior to working in the center, or were provided with training in sign language, as required of all Gallaudet employees. It is certainly not realistic for all genetic centers, which may serve only a handful of deaf clients each year, to have staff members who are fluent in manual communication. Training of genetics center personnel in how to obtain and use certified sign language interpreters, in an appropriate manner, can be very effective. Many health care providers are unaware of legislation (Section 504 of the Rehabilitation Act of 1973) that requires any agency

receiving federal funding to provide "effective communication for hearing impaired persons" (U.S. Department of Health and Human Services, 1982). This legislation stipulates that a range of communication options, including sign language interpreters, telecommunication devices for the deaf (TDD) for communication over the telephone, and written communication must be provided.

The American public is generally not informed about basic genetic principles. Educating consumers about genetics proved to be vital with the deaf community, particularly since more than 50% of that population has a genetic cause for their deafness. The Genetic Services Center has worked to improve the availability of genetics information available to deaf people at all levels. This included working with biology teachers in schools for the deaf to help them incorporate more information about human genetics in their curricula, developing fact sheets on genetics and deafness for general distribution, and the provision of an extensive outreach education effort consisting of workshops and lectures at sites all across the country. These steps have greatly improved the deaf community's awareness about the importance of genetics as a cause of deafness, the process of genetic counseling, and the role of a genetic counselor.

To remove other barriers to receiving genetic counseling services caused by language and cultural differences, the Gallaudet Genetic Services Center developed other strategies that proved to be very effective. Efforts were made to tailor the genetic counseling situation to the needs of deaf clients. This included developing more suitable genetic counseling materials and removing cultural bias from commonly used terminology. Some of these efforts were simple components of the genetic counseling process that often can be overlooked by genetic service providers. The most obvious strategy was to question the deaf clients as to why they were seeking genetic counseling services. The majority of these individuals expressed their curiosity about why they had become deaf and their chances of having deaf or hearing children. When asked about their preferences for deaf or hearing children, most said that they had no preference, but some expressed a strong preference for deaf children who could share their language and cultural values. In genetic counseling training, genetic professionals are taught to be non-directive and to leave their personal biases out of the counseling session. However, many genetic counselors may not be aware of the cultural differences of the deaf client. It may be wrongly assumed that the deaf

client is seeking genetic counseling to determine their risk of having a deaf child. Therefore, to be truly effective, genetic professionals must become aware of the deaf client's value system, which may differ from that of a hearing client. Many tools traditionally used in genetic counseling, such as charts that illustrate patterns of inheritance, are inappropriate in these situations because of the use of culturally loaded terms such as "risk," "normal," and "abnormal." The GSC therefore, developed counseling materials that use the terms "hearing and deaf" and "chance." These small changes facilitate communication and aid in the development of rapport with the deaf client. This sensitivity helps to eliminate some of the cultural biases that may unknowingly occur in genetic counseling, so that it can become a truly non-directive process of information giving. Other publications [4,5] provide more detailed information that is helpful in genetic counseling situations involving deaf clients.

Many of the special considerations developed for use with deaf clients can also be applied to other populations, especially when language and cultural differences are involved. These include the provision and use of qualified interpreters who are not family members, the development of language and culturally appropriate educational materials, the use of genetic assistants and associates who may be part of the cultural group concerned, and educational efforts directed toward consumers, geneticists, and other professionals.

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THE NEW JERSEY GENETIC SERVICE OUTREACH PROJECT

GISELA RODRIGUEZ, A.C.S.W.

The purpose of this workshop is to identify strategies for overcoming language barriers in the provision of genetic services. The objectives are:

- To identify the special language needs of different groups and sub-populations within those groups.
- To propose recommendations for providing for the interpreting and language needs of various sub-populations in the medical genetics setting.
- To propose specific ideas for materials development in different languages and to identify groups that may be able to assist with translation and materials development.

INTRODUCTION

We will discuss the strategies used by genetic service programs to overcome language barriers. The ongoing problems will be identified, and, hopefully during the discussion period, ideas and resources will be shared for the resolution of these difficulties.

The workshop co-leaders and myself, in our work and in our daily lives, are involved in overcoming communication barriers in the provision and acceptance of services. We live in different areas of the country, interact with different populations, and serve in different capacities. It is apparent that there are similarities in communication problems, as well as unique issues and various specific methods employed to overcome these barriers.

STATEMENT OF THE PROBLEM

- 1) Genetic terminology is often culturally biased (e.g., "normal," "defective," "at risk") and genetic information at times is not clearly communicated (e.g., overly complex or culturally irrelevant).
- 2) Translators/interpreters are not given proper training.

THE GENETIC SERVICE OUTREACH PROJECT OF THE UNIVERSITY OF MEDICINE AND DENTISTRY OF NEW JERSEY

Like Gallaudet University's genetic service program, the genetic service center at the New Jersey Medical School has been funded by SPRANS grants from the federal Office of Maternal and Child Health. The purpose of the initial demonstration project in northern New Jersey was to increase services to the growing number of newly arrived immigrants who were found to underuse services in a four-county area. The other goal of the project was to enable the genetic counseling staff to overcome the language, cultural, socioeconomic, and institutional barriers in service provision. The initial project developed strategies and methods that were used at the N.J. Medical School, and at the genetic programs of associated medical centers and outreach clinics. Various strategies were found to be successful and are now being implemented and tested at centers in other parts of the state, where other underserved populations have been identified.

Due to time limitations, this presentation will be restricted to discussion of the N.J. Medical School's experiences and strategies in working with Hispanics, and specifically in overcoming language and cultural barriers. The methods used to enhance services can be adapted to work with other cultural groups. The genetic service centers in New Jersey, especially in the densely populated northeast, see individuals from all over the world. There is a tremendous influx of Spanish-speaking individuals, and the trend is predicted to continue. The Hispanics from the Caribbean, Central, and South America, share a common language, similarities in culture and religion, but vary in their socioeconomic backgrounds which affect their adaptability to life in the United States and attitudes to health care.

When a non-English speaking person came to the N.J. Medical School before the SPRANS project was funded, the genetic counselors and geneticists had several uncomfortable options; either to rely on their own or the patient's knowledge of one another's language and bungle through a session, or use an untrained translator. At times, they used employees of the hospital or the patient's family members. An employee is not an adequate choice because although he/she may or may not be a medical professional, he/she often does not know genetic

terminology, would not have a confident manner of expressing the concepts to a patient, and is often overburdened with translation responsibilities in addition to his/her primary duties. A patient's family member or friend also poses problems when translating, such as possible lack of language skills, limited medical knowledge, emotional ties to the patient, and possible confidentiality dilemmas.

BILINGUAL/BICULTURAL GENETIC ASSISTANT

The genetic service demonstration project attempted to recruit a bilingual/bicultural genetic counselor but was unsuccessful. The problem was resolved by adding a genetic assistant to the genetics staff. This bilingual and bicultural individual was recruited from the local community, and has proven to be an invaluable resource. The genetic aid provides: continuous availability of oral and written translation, avoids misinterpretations, provides the counselor with cultural insights, assists in developing multilingual educational materials, facilitates group counseling by using audiovisuals and handles pre- and post-service follow up calls.

TRANSLATOR TRAINING

Another strategy utilized by our genetics project is training translators who may or may not be genetic service staff. When personnel in a facility is willing to be made available to a genetic service program, the individual is shown audiovisuals, given written educational materials and training sessions are held. A genetic glossary in Spanish and English was developed to fill a gap in reference texts. Everyone who has experienced being "stuck" for a word or explanation knows that a medical dictionary often does not include a new genetic term, and the definitions are far too complicated. The glossary is an easy reference source in the training of bilingual personnel unfamiliar with genetics and also for genetic service providers.

INTERCULTURAL WORKSHOPS

In order to overcome cultural differences and promote communication, the N.J. Medical School's genetic service outreach project has sponsored intercultural workshops and seminars as a method to sensitize the genetic service staff.

These workshops also serve as an outreach strategy. Health professionals and community members are invited to attend along with the genetics staff. Presentations are made exploring family values, religious beliefs, historical backgrounds, and health care attitudes. Genetic counseling cases are used to illustrate a particular cultural dilemma. As a result, members of the community who are unfamiliar with genetic services are made aware of what genetic counseling entails and they get to meet the genetics staff.

MULTILINGUAL EDUCATIONAL MATERIALS

An important aspect of the demonstration project is the development and distribution of educational materials in many languages. There is a tremendous demand for brochures and fact sheets. These materials are needed by health professionals and the public. At the New Jersey Medical School, the outreach staff (geneticist, genetic counselor, project coordinator, and genetic assistant) collaborate to produce the written and audiovisual materials for patient education. The materials are proofread by professionals in the community and tested on consumers.

One of the difficulties in providing appropriate written educational materials is the literacy range of the readers. The clients in our genetic service centers may be sophisticated and in need of detailed information, or may be illiterate and culturally unfamiliar with concepts that the provider takes for granted. It is a common error, when one is developing educational materials, to presume that the reader has prior knowledge, i.e., when explaining cell division you must not assume a person knows what a cell is or that this information is relevant to his or her concerns. Another pitfall is the inclusion of too much information which may frustrate and overwhelm the reader. At times, the Outreach Project has needed to revise materials when after repeated use it is found that the pilot brochure or audiovisual is too complex or needs updating. The Outreach Project uses different materials depending on the client's need. An audio-slide presentation in Spanish, which explains amniocentesis, was developed for individuals who are more responsive to visual information. It is also used for group instruction. The written materials and/or audiovisuals are always used to enhance, and not substitute for, individualized genetic counseling.

WORKSHOP

B. PROJECT FUNDING ON LOCAL AND REGIONAL LEVELS

HOW TO SEEK FUNDS FROM FEDERAL AND PRIVATE SOURCES

HOPE H. PUNNETT, PH.D.

There is a role for activism in improving health care by broadening the availability and impact of genetic services. Clearly it takes money that does not come from fee for services. Therefore one must seek grant funds from either federal or private sources.

The primary source of federal funds for genetic outreach has been the Office of Maternal and Child Health (OMCH), Bureau of Maternal and Child Health at the Department of Health and Human Services. Each year, usually in late winter, there is an announcement in the *Federal Register* of the priorities for which funding will be available. Often there is not much lead time, so it is necessary to be prepared.

For example, the Genetics Section at St. Christopher's Hospital for Children had long been concerned about our interactions with the Puerto Rican community adjacent to the hospital. Working through translators, frequently the children or neighbors of our consultants, we could not know if we were being translated correctly. But five years ago, when the Bureau of Maternal and Child Health and Resources Development announced that it was funding projects to improve genetic services for underserved populations under its Special Projects of Regional and National Significance (SPRANS) Grants, we were unprepared. We needed more time to prepare our application than the deadline allowed. Luckily, the priority continued and by the following year we were ready to write a proposal. We had obtained demographic information to document the need, and then developed our plans for the project. Since we had no official standing or validity in the community, we contacted our neighbors, the local Puerto Rican organizations, churches, and community hospitals, explaining our concerns and our proposal, to obtain their endorsements.

We were not the only project targeting genetic services for underserved populations to be funded by MCH. A review of the active projects for FY 1988 includes, in addition to our own, the following projects in which genetic services for underserved were targeted:

- 1) Genetic services for minority perinatal populations at San Francisco General Hospital;
- 2) genetic services for the deaf at Gallaudet University;
- 3) expansion of genetic services at Meharry Medical College;
- 4) genetic screening, education, and counseling in five statewide family planning councils in Pennsylvania;
- 5) improved utilization of genetic testing and counseling services by Hispanics, Haitians, and Vietnamese in New Jersey;
- 6) genetic services program for Native Americans in Oklahoma;
- 7) genetic services network for Native Americans of the Southwest; and
- 9) thalassemia screening for the Asian community in Boston.

New projects funded in FY 1989 address:

- 1) The needs of the deaf in the tri-state area, New Jersey, Pennsylvania, and Delaware; and
- 2) extension of genetic services to Camden, Trenton, and Atlantic City, New Jersey. MCH annually publishes abstracts of these, and other selected SPRANS projects.

In addition to the direct funding of priority projects, there is a potential, indirect source of MCH funds. The nation is divided into regional genetics networks, i.e., New England, New York, Middle Atlantic, Southeastern, etc. Each of these MCH regions has its own organizational structure and applies for MCH funding with its own needs in mind. Each network has evolved differently. Mid-Atlantic Regional Human Genetics Network (MARHGN) with its early start and unique depth of resources, has encouraged the development of small educational and demonstration projects within the region that compete for MARGHN funding. This symposium originated as a MARHGN activity. Projects involving one underserved group—children in foster and adoptive

care—have been targeted and funded by that population's advocate in the region. Other regions have not incorporated the funding of small projects in their fiscal planning. Again, activism by members of networks could open up the process or change the priorities. By becoming a participating member of a regional network, one can influence how it allocates its money.

Finally, in addition to the SPRANS money, there is federal money in the form of Title V Block Grants that goes directly to each of the states. It may be possible to apply for funding depending on a state's priorities. There may also be line items in the state's budget for health that may be already available, or be made available by dint of active campaigning. In Pennsylvania, we have been fortunate in having a health department that supports genetic services for the economically underserved, as well as awarding a grant for counseling of the deaf, which complements the SPRANS grant. Other states may have other funding opportunities.

Funding opportunities also exist in the form of grants from private foundations, particularly those that have improved health care as an objective. How does one find such sources of support? There are two major directories of foundations available in reference libraries. The Taft Group publishes a multivolume directory. The Foundation Center is an independent national service organization established by foundations to provide an authoritative information source of private, philanthropic giving. It maintains four major reference collections (New York, Washington, D.C., Cleveland, and San Francisco) and has a national network of cooperating library collections, as well as a toll-free number (1-800-424-9836). The Foundation Center publishes an annual *Foundation Grants Index*, *Source Book Profiles*, and computer search printouts derived from the Center's grants data base of foundations that report their grants directly to the Center. *Grants for Hospitals and Medical Care Programs* lists 2,646 grants of \$5,000 or more made by over 300 foundations. Both large and small organizations are listed, with their goals, restrictions, amount of money given annually, size of grants, contact person, etc. In the listing by populations served are Asian Americans, blacks, handicapped, Hispanics, Native Americans, and minorities.

Grantsmanship requires imagination, taking the avowed interest of the foundation, and finding a way to make your project adapt to it. Do research in

advance, determine the interests of the foundation, and if you don't qualify, don't apply. If in doubt, discuss the project with the foundation's contact person.

On the positive side, many foundations have funds that they are unable to disperse annually because of the restrictions placed by the grantors. Limitations often include subject area, recipient type, ethnicity, or geographic location. Ideally, find the restrictions to use to your advantage. If you need to show community involvement in or support for your project, contact the key persons and obtain letters of endorsement from them prior to writing the grant. You may want to present them to the contact person with whom you have made an appointment. If you need collaborators, line them up, if possible, in advance.

Finally, remember that success in achieving funding may require repeated attempts. If a proposal is not funded, find out why and reapply if possible. It is difficult not to be discouraged when unsuccessful, but grantsmanship is a skill to be practiced and perfected. Luck helps, but hopefully perseverance pays off.

FUNDING AVAILABLE THROUGH THE MARCH OF DIMES

ALICE NOVITSKY

The March of Dimes Birth Defects Foundation awards grants for health services and research. Qualified applicants from universities, medical schools, hospitals, health agencies, and community institutions, are invited to submit proposals for programs directed at the prevention of birth defects.

For all grant programs, a letter of inquiry and a 300-word abstract of the proposal must be submitted before an application for a grant will be provided. The March of Dimes defines a birth defect as an abnormality of structure, function, or metabolism, whether genetically determined or a result of environmental influence during embryonic or fetal life. Low birthweight is included within this definition. A birth defect may cause disease from the time of con-

ception through birth or later in life. The interests of the March of Dimes include the broader aspects of pregnancy outcomes, i.e., factors underlying the birth and survival of a healthy infant.

The following research programs are offered by the March of Dimes:

- 1) Predoctoral Graduate Research Training Fellowship—available to Ph.D. candidates who have the potential for successful research careers in birth defects prevention. Students must be entering or in their first or second year of graduate work, and be recommended by deans or preclinical department heads.
- 2) Basil O'Connor Starter Scholar Research Awards—designed primarily for young investigators (M.D.s or Ph.D.s) who are interested in embarking on independent research after completion of their doctoral or post-doctoral training.
- 3) Summer Science Research Program for Medical Students—available to all U.S. medical schools each calendar year.
- 4) Basic Research Program—funding for research on new preventions, treatments, and cures of birth defects.
- 5) Clinical Research Program—available for studies of humans to learn what can be done to prevent or treat birth defects.
- 6) Social and Behavioral Research Awards—available for studies of medical, psychological, social, and familial factors that affect the development of children who have birth defects.
- 7) Reproductive Hazards in the Workplace, Home, Community, and Environment—awarded for the investigation of possible hazards in the workplace and environment that may cause birth defects.

All inquiries regarding March of Dimes support of local, state, or regional programs should be directed to this address:

Grants Administration
March of Dimes Birth Defects Foundation
1275 Mamaroneck Avenue
White Plains, New York 10605
(914) 997-4552

In addition to the research programs of the March of Dimes, funding may also be available for regional and local programs with the following objectives:

- 1) To provide prenatal and perinatal care for pregnant women and newborns, and genetic services for families at risk for birth defects;
- 2) To provide and stimulate the development or expansion for basic and continuing education of health professionals involved in perinatal care; and
- 3) To provide and stimulate the development or expansion of education programs to instruct and motivate parents and prospective parents, students, teachers, patients, and the general public. Grants are made to schools, health agencies, and other community institutions with the objective of preventing birth defects and improving the outcome of pregnancy.

In addition to monetary support of programs, the March of Dimes may be able to lend technical assistance through staff or volunteers; print materials for public health and professional education; and provide audiovisual aids. The March of Dimes is particularly interested in collaborating efforts, such as co-sponsoring professional conferences. Funding priority is given to new programs that need seed money; March of Dimes funding for the program is usually limited to three to five years.

LOCAL FUNDING: THE OHIO EXPERIENCE

ELIZABETH WISDOM

The Ohio Department of Health employs a full-time staff unit to provide administration and monitoring of grants awarded to 10 genetic and 10 sickle cell projects statewide. These services are extended on a regional basis and cover educational, screening, and counseling activities.

To discuss an actual proposal, the appropriate contact person would be the program administrator for genetic services or the chief of the Division of Maternal and Child Health.

An area that is considered a priority is newborn screening for sickle cell and other genetic diseases. Of equal importance would be projects such as installing a laboratory system capable of keeping track of screening results, and gaining increased cooperation from hospitals in conforming to protocols for newborn screening.

The Ohio Sickle Cell and Health Association (OSCHA) received a one-time award of \$25,000 from the governor through a special fundraiser last fall. The Ohio Sickle Cell Affected Families Association received \$500 from this money. As this was a one-time allocation, discussion of an actual proposal would be inappropriate. The two areas that the OSCHA considers priorities are education and advocacy.

The Sickle Cell Awareness Group (SCAG) of Greater Cincinnati, Inc., receives an annual award from the United Way of Cincinnati. Allocation for the current fiscal year was \$190,679 to pay a staff of five persons. The staff's mission is to promote and nurture coping skills, self-sufficiency, and healthy lifestyles among affected families and individuals, and to provide factual information about sickle cell disease and other red blood disorders to all segments of the greater Cincinnati community.

To achieve these goals, four programs are offered: community health education, special educational opportunities, peer education and counseling, and social work and outreach. The parents cell patients were organized in 1970. They are a significant part of this agency and its history. I am proud to be a board member. The SCAG does not award funds to other groups. However, their services are extended to cover the categories mentioned above.

The Cincinnati Comprehensive Sickle Cell Center is among those research and demonstration grantees funded by the National Institutes of Health. This project is not a resource for funding other genetic projects. Their technical assistance is utilized statewide. Their knowledge and leadership are sought by professional groups locally, statewide, and nationally.

Of special note is the Cincinnati Comprehensive Sickle Cell Center's annual sponsorship of a SCAG member to attend the annual meeting of the National Sickle Cell Disease Association.

The Great Lakes Area Regional Genetics Group received a SPRANS grant in the amount of \$170,000 for fiscal year 1989. These funds are earmarked for travel and staff expenses for the six state regions; awards are not made beyond the steering committee and subcommittees. The general goal of the Great Lakes Area Regional Genetics Group is to broaden lines of communication within the genetic community.

WORKSHOP

C. LEGISLATIVE ACTIONS—FOCUS ON THE LOCAL (SPONSORED BY THE MARCH OF DIMES BIRTH DEFECTS FOUNDATION)

EDUCATING LEGISLATORS ABOUT GENETIC SERVICES

MARY ANN WILSON

In 1981, the federal government implemented the concept of block grants, which would be awarded to states to fund categories of programs. Genetic services were, and continue to be, included in the Maternal and Child Health (MCH) Block Grant. When this happened, there was an immediate decrease in funds overall for genetic services. The block grants became politicized as competition for funds allocated for local programs increased, and reporting and accountability requirements for the states receiving the federal money decreased.

The recent breakthroughs in biomedical research, particularly in the field of genetics, have provided the evidence needed to increase funding for research and genetic services.

The focus should be primarily on the state legislators and governors to ask for genetic services, appropriate funds, and monitor those programs for effectiveness. Sometimes it takes only one family affected by a genetic condition to gain the attention and concern of the local state representative to put a service program in place.

An articulate family member and/or physician knowledgeable in genetic services, who is willing to volunteer a large portion of their day to publicly testify before the state legislative committee and provide written statements, greatly contributes to educating the legislators and staffs on the need for biomedical research on the national level and genetic services on the state level. Keep in mind that legislators often move from the local level to the state, then to the national arena in their political careers.

Voluntary organizations can help by providing comprehensive information, including numbers of people affected locally and nationally, and training in working the legislative process.

One of the effective ways of educating the legislators is by making concise, accurate, strong, well-rehearsed presentations to the health aides by no more than three people. Timing is crucial. The presentation should be given during the legislative session, and just before the authorization or appropriation bills are to be finalized, depending on the particular to be addressed.

Make sure that key legislators (state and national) from your district are on your organization's mailing list. Automatically send local newspaper clippings about your genetic disorder or organization to your government representatives. This helps to build up rapport with the legislators and to keep them informed "on the homefront." Attend local council and town meetings to express your support of genetic services and various issues that affect your family's life, as well as your concerns. Better still, serve on panels, committees, commissions, boards, etc., where significant decisions are made on issues that have an impact on your life.

Never underestimate the power of a short, timely letter focusing on one issue and how it affects your family or the people your organization represents. Always keep a copy of your letter and ask for a response.

To be effective in educating Congress, the state legislature, or the local hospital board, an individual or an organization must be knowledgeable about his or her disorder and organization, and know the needs of those affected. Remember, you are the expert in this area.

By working with the key players through the legislative process locally, then at the state level, and continuing to the national level, you can make a difference for all who are affected by genetic conditions.

WORKSHOP

D. USING THE MEDIA TO PROVIDE PUBLIC EDUCATION ABOUT GENETIC SERVICES

DESIGNING PUBLIC EDUCATION BROCHURES TO REACH LOW LITERATE AND MINORITY PERSONS

TRISH MAGYARI, M.S.

Public education brochures are often a consumer's first contact with a genetic service center or a genetic support group. To be as useful and appropriate as possible, written materials need to be readable and culturally sensitive. Here, we will consider challenges and strategies for overcoming the potential barriers to reaching low-literate and minority populations through public education brochures.

SPECIAL POPULATIONS

Low-Literate Populations

A substantial proportion of the general population has difficulty in understanding technical written information. It is estimated that approximately 50% of all Americans read at the 10th grade level or less, and approximately 30% read at the 7th grade level or less. In addition, the Department of Agriculture has recently determined that only health education materials written at the 6th grade level or less are appropriate for the recipients of the Supplemental Food Program for Women, Infants, and Children Program (WIC).

Minority populations

The minority population in the U.S. is estimated to comprise approximately 20% of the U.S. population, including persons of minority cultures, ethnicities, and racial groups as well as non-English speaking populations.

Low-literate and minority populations are not the same. There are many minority persons who are not low-literate, and many low-literate people who are not minorities. Therefore it is important to keep the two concepts separate.

DEVELOPING MATERIALS

Reaching our goal of developing readable and culturally sensitive brochures depends on having a well-thought-out plan. The plan includes defining the project, setting goals and objectives, defining the target population, deciding upon the particular education materials to be produced, and developing a distribution plan. Of all the elements of the plan, defining the target population is probably the most crucial in regards to reaching low-literate and minority populations. If the target population includes both professional and consumer groups, keep in mind that brochures at the college level (appropriate for professional population) may not be understood by many consumers.

CULTURAL SENSITIVITY

Below are several guidelines for reaching specific ethnic, cultural, or minority groups with culturally sensitive and acceptable materials:

1. Involve members from the target community and other agencies working with the target population in the development and implementation of a public education program. This will insure that all materials are culturally sensitive and acceptable. Having other agencies aid in the development or review of the materials also makes distribution easier, as you will have already established contacts in the community.
2. Have materials reviewed for cultural sensitivity. Solicit review of materials from professional peers, patients, and other agencies that are working with the same target population. These draft reviews can aid greatly when it is time to field test materials.
3. Design materials so that they are appealing to the target population. A simple way is to depict persons from the population in your brochures, either by illustration or photographs. Using particular colors, designs, or symbols that are familiar and significant to the population can make the brochures more appropriate and acceptable.

DECREASING THE READING LEVEL OF WRITTEN MATERIALS

If the target population is a low-literate one, then the materials need to be written at the 5th grade level or lower. When writing materials in another language, it is important to remember that not everyone who can speak that language can read well. This means that simply translating the materials from English to Spanish will not necessarily allow everyone who speaks Spanish to read them. If your population is an immigrant or a refugee population from rural Central America, the persons in that population may have only a few years of formal schooling. Therefore, low-literate materials will be appropriate.

When writing health education materials for the general population, it is prudent to aim at approximately the 9th to 10th grade reading level (or lower). Below are some general guidelines:

1. **Use short, simple words and sentences.** Because of the amount of technical information that can be expected in a genetics-related brochure, and the high number of new concepts that may be introduced, it is best to keep sentences to 10 words or less. Most readability scores evaluate the number of times words with three or more syllables are used in a sentence. Therefore, each time you use a three-syllable word, ask yourself, "Is there a shorter and more familiar word that I can use to replace this longer one?" For example, "is a progressive disorder" can be modified to "gets worse over time."
2. **Use the active voice rather than the passive voice.** For example, instead of writing "This family history form must be returned in order for an appointment to be made," say "Please fill out and return this family history form if you want us to make you an appointment."
3. **Use conversational style:** Write down the words normally used to explain a topic to a new family. Avoid writing to impress your peers.
4. **Be concrete, not abstract.**
5. **Be direct and to the point.** Begin paragraphs with a simple topic sentence. Sometimes it helps to put the topic sentence in bold print and write it in a larger type size. In this way, persons who have lower reading skills will be able to pick out the important information. Do not

include unnecessary or irrelevant information in the topic sentence. Try to say exactly what you mean. Avoid words like “seems,” “may,” “perhaps,” “possibly,” “generally,” “usually,” and “apparently,” as they confuse low-literate readers. Also avoid wordy statements such as “You may wish to make an appointment.” Say instead, “Please call to make an appointment.”

6. **Avoid hyphens and contractions.** Words split with hyphens and contractions are more difficult for persons of lower reading skills. Avoid them whenever possible.
7. **Do not right justify.** Although right justified materials look professional, they are very difficult to read for persons who have low reading levels.

Producing materials with a readability score at a low level does not necessarily insure their readability, as other factors not usually evaluated by readability scores must also be taken into account. These factors include: type size, type style, concept density, amount of information, number and type of illustrations or graphics, and use of technical/medical terminology. These points are described below:

1. **Type size:** A 12-point type (about six lines to the inch) is recommended as a minimum for low-literate populations. A 10-point type, such as is found in many genetics brochures, is difficult for marginal readers. A 9-point type (fine print) is simply too small for many poor readers to attempt to read. (This book, for example, is printed in 10-point type: Editor.)
2. **Capital letters:** Even for good readers, capital letters are hard to read. To emphasize material, use a larger type size or underline. Capital letters should be used only where grammatically correct, such as at the beginning of a sentence, or in a title.
3. **Type style:** Upright serif type letters are easiest to read. Avoid italics as these are harder to read. Serif type letters (those with ‘feet’) are easier to read than some sans-serif type.

4. **Concept density:** This refers to the number of new concepts that are introduced in any sentence or paragraph. Limit the number of new concepts, especially in the first sentence and the first paragraph.
5. **Amount of information:** It is important to limit information to main points. Many public education materials contain an overwhelming amount of information. This is due partly to small type size and a lack of illustrations or graphics. A solid page of writing often discourages readers. Decide ahead what the main points are and limit the materials to these. Extraneous material, such as the history of the delineation of a particular disorder, is unnecessary. Because it is important to limit the amount of information and the number of concepts on each page, it is often more useful to produce a small booklet than a 9 x 11 inch foldout brochure.
6. **Illustrations:** Illustrations make materials more interesting and thus acceptable to lower reading populations. Use picture, subheads, and defined graphics.
7. **Define technical medical terminology:** Define all words not part of the general knowledge base of the target population in simple, lay terms.

FIELD TESTING

If you have developed materials using all the guidelines above and want to insure that they will be useful and appropriate, then field testing the materials will be worth the time and effort. This means that members of the target population formally evaluate the materials. Field testing is a systematic way of finding out if the message is coming across to the users with the intended meaning. It identifies elements that could be changed to make a message more effective. Components of field testing are attraction, comprehension, demonstration, self-involvement, acceptability, and persuasion. Written materials and visuals can all be field tested.

REFERENCE:

- Doak, C, Doak, L, Root, J. 1985. *Teaching patients with low literacy skills*. Philadelphia, PA: Lippencott Company.

PUBLIC EDUCATION THROUGH THE MEDIA

FLORENCE NEAL-COOPER

Public education is the panacea for a well-informed public, and should aim to reach, inform, and influence the public in a positive manner. Education is the key that determines how effectively individuals will accept, understand, apply, identify, and utilize the information and /or services available.

In order to accomplish an effective public education program through the media, there are several important strategies to use:

1. **Selecting a good public relations person.** One who is enthusiastic, very knowledgeable about the specific topic, active in policy and programming decisions, and has some writing or communication skills. This person may be a member of your agency or you may need to seek an outsider.
2. **Identifying and knowing the audience or public that you want to address** will be helpful in developing your materials.
3. **Determining objectives.** What would you like to see accomplished? This will enhance the effectiveness of your presentation.
4. **Establishing priorities,** and working on them in the order of their importance and timeliness will fulfill your objectives.
5. **Working within the budget.** If you have to work within a budget, you must be sure that your objectives and priorities are reasonable, and that you can accomplish them successfully with the amount of money that is available.
6. **Selecting a technique or techniques** that will assure the best results for you. There are numerous basic publicity techniques that you may wish to use, especially if you want to saturate the public with information.
 - A) News releases
 - B) Feature stories
 - C) Photographs

- D) Radio and T.V. appearances
- E) Public service announcements (PSA)
- F) News conferences/press releases
- G) Letters to the editor

You may want to use several of these techniques (appealing to all forms of the media) that support each other, or you may just choose to use one method for promoting your activity or program. When utilizing any of these techniques, your aim should be to get the message across to the public.

NEWS RELEASES

When writing a news release for the printed media, the information should be tight with the facts, well organized, accurate, newsworthy, and not lengthy. The media does not take well to releases that give the impression that they are disguised advertisement or present opinion rather than fact.

You want your readers to understand why this genetic information is important to them and how it can benefit their life style. The key to a well-written release is the lead statement. This is where you must grab a reader's and editor's interest while giving the essential facts of the story. Make your lead as interesting as possible but keep it short. Follow your lead with essential information, written in short, concise sentences. Paragraphs should be no more than three or four lines long (one page is best). Stick to the facts, minimize the adjectives, do not editorialize; opinions have no place in news stories. If you need to be opinionated, use direct quotations.

An acceptable news release should be structured in the following manner:

- 1) Who, what, when, where, why
- 2) Important details
- 3) Miscellaneous information

News releases should always be typewritten on plain, white, 8 1/2 by 11 inch paper. If you are sending multiple releases, send clear xeroxed copies.

FEATURE STORIES

Features are stories that explore situations, events, and trends that have special human interest and mass appeal. A feature story appeals to the heart as well

as the mind. Media outlets are interested in feature story ideas. Newspaper and magazine features take time to research and write properly, consequently most editors prefer to assign their own people to feature stories. When planning for a feature story about genetics and genetic services, use these timely tips to ensure that your story gets published.

- Identify the feature editors or news directors, and call or write to suggest your feature. Never appeal to more than one editor at a time.
- Follow-up with a one-page letter outlining your proposal.
- Use the most colorful and meaningful facts, and organize them well.
- Use people when appropriate; human subjects always make good copy because they appeal to the public and editors always aim to please their audiences.

Because feature stories are more complex than news releases, they tend to be longer and therefore will require more time and preparation.

PHOTOGRAPHS

A newspaper photograph can often provide more publicity value than a newspaper article. Editors love good photographs and will frequently run a photograph of an event even when it lacks the newsworthiness for a story. The easiest, most effective, and least expensive way to handle photography is to have the newspaper do it for you. You must convince the editor that your story is important enough to assign a photographer to cover it. Be sure that you are on the scene to assist the photographer and provide the necessary information.

If you must supply the photographer, hire a professional photographer—one who has quality and style and who has done press work before. If you are not familiar with a pro, the newspaper photo editor can suggest one.

Action shots tell the story better than one of a group of people sitting or standing. If the photograph includes people not directly associated with your agency, get their permission to use the photo for promotional purposes and have them sign a photo release. Captions should always describe what is happening in the photo and should not leave the viewers wondering what is going on. Unless an editor requests something different, photos for publications should always

be an 8 by 10 inch black-and-white glossy print. Never use paper clips or staples on a photograph, and never write on the back of a photograph.

RADIO AND TV APPEARANCES

The broadcast media have enormous reach, scope, and impact. Television has an unmatched capacity for conveying action and commanding attention. Radio reaches listeners everywhere all of the time. Television and radio want to provide their audiences with news, information and entertainment. There are a number of formats utilized by the media that might fit your agency's needs.

- Live or recorded interviews
- Panel discussions
- Talk shows and personality spots
- One-time shows on the specific genetic service
- Public service announcements
- Newscasts
- Community calendar or bulletin boards
- Editorials

Before making contact with the television or radio station, study the various types of programming that the station offers and determine how your agency can best use the service. When your agency decides to use television or radio to promote your genetic services there are a number of strategies that you should employ for a successful production.

- **Making Contact**

Be sure to call the station and determine the appropriate person to deal with, especially if it is a person other than the producer of the show. Try to meet with the producer, introduce yourself and your agency, and explain your services and their importance to the public. Make a friendly appeal for their cooperation and assistance. Ask about the format and what is required of your agency, how they want the materials prepared, what audiovisuals are necessary, and, most importantly, what their listeners or viewers want.

- **Identify a good spokesperson from your agency**

One of the best methods for gaining access to television and radio is to provide them with well-informed and interesting people who can effectively discuss your agency and the issues of concern. Be specific and tell the producer exactly how you think your spokesperson can best do the job, because your agency should know the resourcefulness of the spokesperson. You may suggest props, demonstrations, or other situations; however, do not be dismayed if the producer rejects some of your ideas and wants to make changes: remember that he or she is the expert, and knows what will be the most effective route to pursue.

- **Be prepared**

Coach your spokesperson through mock interview situations. Try to think of tough questions that may be asked and think through the possible answers. Make sure that most questions can be answered fairly quickly, within 20 seconds. Some producers may give you a list of questions that will give you the opportunity to practice the answers within the time frame.

- **Be mindful of timing**

Be sure that all necessary materials are in the producer's hands on the requested date. Make sure that your spokesperson is at the station in ample time for a taped or live interview. The producer will let you know the exact time.

- **Letters of thanks**

Do not forget to send letters of thanks to the appropriate station personnel. Let them know that you appreciate their interest and cooperation, and fill them in on the results achieved.

- **Public service announcements (PSA)**

Television and radio donate a certain amount of free time to public service programming for worthwhile nonprofit agencies.

A PSA is prepared information that explains the nature of the problem and/or the services that are available through your agency. This informa-

tion should have good audience appeal and must be timed according to the regulations of the station. The time frame for most PSAs may range from 15 to 60 seconds. PSAs that call for action or that offer a service have greater appeal to broadcasters.

- **News conferences**

A news conference is a dramatic way to announce an important story and its primary purpose is to answer questions. However, it should be reserved for those special occasions when the topic is too complex to be covered in a news release or when its impact might otherwise be lost. Plan the news conference well in advance and make sure that it is timed for maximum publicity value. Usually the station will decide the best time for maximum publicity value.

- Notify the media at least two weeks in advance.
- Contact the editor or news director through a "notice of press conference." Briefly state the subject, purpose of conference, and the participants.
- Follow up the notice with a phone call.
- Estimate the number of people likely to attend; arrange for a room large enough to seat them comfortably, allowing for the media equipment.
- Always prominently display your agency's logo and name, so that it can be included in pictures of the conference.
- Provide plenty of background materials, including news release about the agency or topic to be discussed, for reporters to use in their stories.
- Try to arrange to have telephones available, if possible. It is a good idea to provide some simple refreshments.
- Be available for questions and answers.
- A news conference should be no longer than 30 minutes. Participants should address the reporters and then ask for questions.
- After the conference, the participants should remain for exclusive interviews with key media people.

- Be as cooperative as you can.
- Evaluation and follow-up.

The communication process is one of continued feedback and evaluation. You must know if you are reaching and impacting your audiences. Talk to people, solicit reactions through questionnaires or interviews. Find ways to measure your responses. Build evaluation of your agency's efforts into the plan, for it is through evaluation that you can determine your future actions in utilizing the media. If there is a media society in your locality, it would be advantageous to your agency if you attended their workshops. I also recommend obtaining a copy of the *Publicity Handbook* and the *Public Affairs Handbook* from Consumer Services, The Sperry and Hutchinson Company, 2900 West Seminary Drive, Fort Worth, Texas 76133, which provided information contained in this presentation.

WORKSHOP

E. REACHING GEOGRAPHICALLY ISOLATED POPULATIONS

PROVIDING GENETIC SERVICES IN PUERTO RICO

MARIA A. TORO-SOLA, M.D.

Ten years ago, at the Sickle Cell Projects Annual Meeting in San Juan, I had the opportunity to present the status of genetics in the island. At the time, it was an uphill course to change the minds of hospital administrators and health professionals to "think genetics." We needed to modify academic interests and attitudes of the house staff towards the patient with congenital malformations, mental retardation, families with genetic diseases, and the concept of prevention through genetic counseling. We must acknowledge that changes have occurred.

DEMOGRAPHY

Puerto Rico is an island so small (39 miles by 111 miles) that the smallest state is two and a half times its size. A great percentage of the island has a mountainous topography.

There were 3,223,000 Puerto Ricans in 1976 [1]. To the demographer's surprise, the expected large population growth for the 1980s did not occur, and the population remained stable. This is explained by the success of family planning programs, as well as migration of islanders to the mainland. The characteristics of these emigrants has also changed. In the 1950s, low-income, unskilled workers moved mostly to New York City, seeking better opportunities. The new emigrants are professionals constituting a "brain drain," as well as retirees seeking tranquil environments in different regions of the U.S.

ETHNICITY

Puerto Rico is a mixture of ethnic groups. Its original inhabitants were Taino Indians. In 1493 the Spaniards came to the island, and by the 16th century

the native population had dwindled. African slaves were introduced, and their descendants settled the coastal towns, while those of Spanish ancestry populated the mountains. Because of these facts, there are geographic characteristics for genetic diseases in Puerto Rico. Slavery was abolished in 1873, although by that time many slaves had become free. Interestingly, the city of San Juan has a mountainous sector called Caimito. Many freed slaves settled the area, establishing in the capital a geographically isolated population with inbreeding, and thus, the prevalence of genetic diseases.

After the 1960s, other groups, such as Cubans and Dominicans (who constitute a high percentage of our illegal population), arrived in large numbers. A population of Arabs, Chinese, and Haitians are also enriching our genetic pool.

POLITICS

The island is a commonwealth with U.S. citizenship. We are the third consumer in the world of U.S. goods, and our men and women serve in the U.S. Armed Forces. Within the next four years, we are expected through a plebiscite to select by a majority of votes, whether to remain a Commonwealth, become the 51st state, or become independent.

DELIVERY OF GENETIC SERVICES

Neonatal Screening

The Sickie Cell Project was established in 1977 directed by a pediatric hematologist. It was the first attempt to organize and deliver genetic services on a larger scale. There were two genetic sections at the time, one in the San Juan City Hospital and the other in the University Children Hospital. Both institutions are localized in the Puerto Rico Medical Center. Fourteen percent of the total island's births took place in their nurseries. The first screening tests were for hemoglobinopathies. In 1980 hypothyroidism screening was introduced followed by PKU in 1981. The Council for Genetic Diseases was created by the Governor and mandatory screening is in effect since May 2, 1989. For neonates born in San Juan and the northeast of the island, hemoglobinopathies screening is also mandatory. This is due to the greater incidence of these genetic diseases in immigrants from the Dominican Republic, who mostly settle in San Juan and northeastern Puerto Rico.

Other associated programs have developed within the original, such as the recently created metabolic screening laboratory and the hemophilia project, with a satellite clinic in the center of the island where family clusters are seen. Although financing for research is difficult to obtain, the Commonwealth provides funds for the neonatal screening projects; the Developmental Disabilities Council evaluates and approves research proposals.

Prenatal Screening

Because of our chronic lack of funds, we devised an alternate option for the delivery of genetic services to the at-risk pregnant woman of San Juan. Together with the Departments of Obstetrics, Nuclear Medicine, Social Service, and the hospital's director, we offer counseling, and amniocentesis procedures, and send the fluids to Dr. Hope Punnett's cytogenetics laboratory in Philadelphia. The costs are paid by the hospital, and this is the only program geared to the indigent pregnant female in Puerto Rico. A new alpha-fetoprotein screening program for neural tube defects has started recently.

Counseling and Diagnosis

Both genetics sections at the medical center offer genetic counseling and diagnosis. The cytogenetics laboratory at the San Juan City Hospital is the only such facility in the island. Patients are referred from metropolitan San Juan as well as other areas. At present, with funds from the Developmental Disabilities Council, we are conducting research on the fragile-X syndrome. Through a special clinic and outreach, we have identified 20 families as fragile-X positive. Our research is in its fourth phase.

STRATEGIES: PRESENT AND FUTURE

San Juan is the biggest municipality of the island. Its population was 425,749 in 1987. We are expecting a population drop by the year 2000. The adjacent municipalities are growing steadily and touching the big city's boundaries. Because of the characteristics of San Juan's population, our child mortality rate is higher than for the rest of the island, 16.8%. Compared to the rest of the island, the San Juan City Hospital receives 60% of the indigent population. Alcoholism, poor nutrition, and drug addiction are rampant. AIDS is also tak-

ing its toll among women and children. We must engage in a vigorous campaign for education of citizens, specially pregnant females, in regard to all of these complications. The city has elaborated strategies for the year 2000 to decrease infant mortality to less than 14%.

Genetic diseases are presently a priority for central and local island governments. Developmentally disabled citizens now constitute 10% of the total population. More and better services are being created for this population at a public and private level. New professionals, such as developmental pediatricians, are involved in the health care of the disabled. As infectious diseases and obstetric complications diminish, genetic diseases will surface. We are preparing for the new era of prevention through education, diagnosis, and early treatment.

OVERVIEW

Great progress in genetic diagnosis and counseling in Puerto Rico has finally happened. These changes took ten or more years but the needed programs for screening, prenatal diagnosis, counseling and diagnosis for mental retardation syndromes and other disabilities are now part of our health systems. The public is aware of their risks and the priorities of central and local governments are changing. The future must bring continued support providing funds and incentive for researchers in order to reduce the "brain drain." More outreach is needed by creating satellite clinics through the cities. This is the only hope to effectively deliver the best services through a genetic network.

A MODEL GENETIC OUTREACH PROGRAM TO MEET THE NEEDS OF GEOGRAPHICALLY ISOLATED POPULATIONS*

BARBARA DIXSON, R.N., M.N.

There is a large population at risk for having children with genetic disorders in San Diego and Imperial counties in California, who do not utilize existing resources because of various barriers including culture, language, and geographic isolation. These two counties are the southernmost region of California that borders Mexico and has a population of 2 million. San Diego is one of the fastest growing areas in the country due to migration from other parts of the United States and other countries. It is the seventh largest city in the United States with a large metropolitan area, yet over half the population of San Diego County lives in smaller communities, and most of Imperial County is rural. San Diego has excellent genetic services; however, they are centralized in the city and therefore not readily available to everyone. The genetic centers do not have the resources to reach out to underserved populations.

Due to the close proximity to Mexico, there is a large Mexican-American population in the region. The 1980 census identified 14% of San Diego County and over 50% of Imperial County as Latino or Spanish-speaking. There is a large population of migrant workers in the agricultural areas of both counties. The mobility of this group and the counties' extensive rural areas compound the difficulty in assuring availability of genetic services.

In addition to the migration of Mexican-Americans into the area, San Diego has been a major relocation area for Southeast Asian refugees. Approximately 6% of the county's population is Southeast Asian, and nearly all live in the metropolitan area of San Diego. Many of these families speak little or no English. American customs and medical resources are foreign and in many cases

* SPRANS Grant #MCJ061003, Maternal & Child Health Division, Bureau of Health Care Delivery Assistance.

frightening to them. Due to language and cultural factors, and because there was no bilingual genetic specialist in the area, these groups had not been served successfully.

In an effort to serve these groups, the San Diego Regional Center for the Developmentally Disabled obtained a federal grant (SPRANS/MCH Grant #MCJ-061003) to implement a model genetic outreach program. This project had four goals:

- 1) To demonstrate innovative mechanisms to increase access to and utilization of genetic services by underserved minorities and persons in rural areas at high risk for genetic disorders;
- 2) To increase knowledge of genetic conditions and resources in professionals and paraprofessionals serving the target populations;
- 3) To increase knowledge of genetic conditions and resources in the target populations; and
- 4) To evaluate the effectiveness of the project and disseminate information regarding the project.

This presentation will focus on the first goal, which was to develop innovative methods of reaching persons in rural or isolated areas, as well as to provide genetic services to culturally and linguistically diverse populations. Successful networking with multiple agencies in the two-county area that already serve these groups was the key to achieving this goal. The most effective working relationships were developed with the community perinatal clinics, the Public Health Department, the WIC Program, the Union of Pan Asian Communities, the maternal serum alpha-fetoprotein screening program (MSAFP) and the two major prenatal diagnosis centers in our area.

To improve access to services, the staff went out into the community and provided on-site genetic counseling to patients, and genetic consultation to professionals and paraprofessionals in clinics and on home visits. Satellite genetic clinics were conducted at the health department and at two prenatal clinics in Imperial County and two in San Diego. Financial assistance for transportation to the genetic center for genetic testing was provided on an as-needed basis.

A toll-free line was established to encourage calls from outlying areas, and a poster was developed and distributed to advertise multilingual, multicul-

tural genetic services, and the toll-free number. Slide presentations about teratogens, prenatal diagnosis, and basic genetics were presented to Southeast Asian women at WIC programs. Slide presentations were also made to small groups of Vietnamese and Spanish-speaking parents of developmentally disabled children, pregnant women in prenatal clinics, and professional staff, including physicians, social workers, Head Start teachers, and public health nurses.

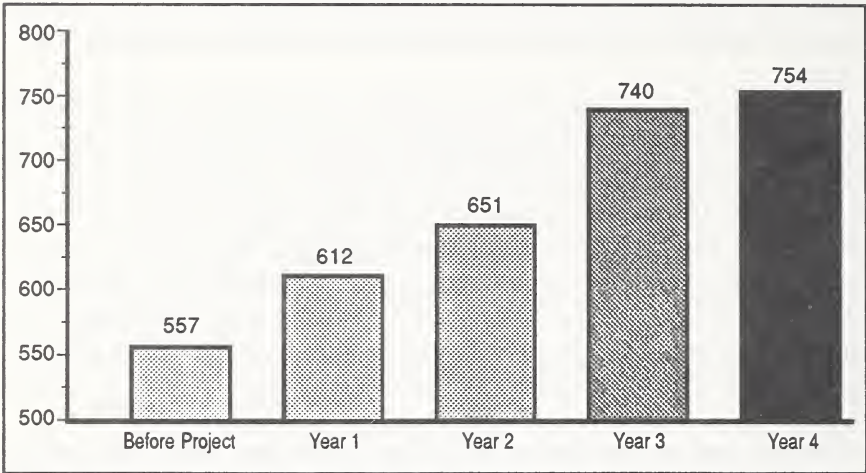
Three very basic pamphlets on prenatal diagnosis, MSAFP screening, and genetic counseling were developed in English, Spanish, Vietnamese, and Laotian. Seven newspaper articles in English (2), Spanish (1), and Vietnamese (4), have been published on prenatal diagnosis and genetic counseling. One talk show interview was done on the San Diego Spanish language radio station. A display board was developed and has been used at several health fairs and conferences along with written materials to promote an awareness of genetic issues and services. The last materials to be developed were small flip charts with pictures and text in English/Spanish and English/Vietnamese to be used in counseling individuals or small groups about ultrasound and amniocentesis.

The success of this project can be most readily demonstrated by a few simple statistics (tables III-1 and III-2), starting with a baseline of the average number of clients served during the two years preceding the start of this project. It is easy to see the increases, not only in total number of families served, but in the geographic location, ethnic composition, and primary languages of those clients.

The total number of cases increased by 35%, which was expected with the addition of two new staff members. However, the dramatic increase in the number of clients served in Imperial County clearly indicates success in reaching this population, where the number of cases nearly tripled by the fourth year of the project. The number of referrals from the outlying areas of San Diego County also increased significantly and is reflected in the number of Latino families served.

Although the number of white non-minority clients stayed approximately the same during this period, the number of Latino clients increased from an average of 81 to 231, and the number of Asian clients rose from 10 to 82.

**Table III-1: Number of Genetic Counseling Cases
Opened by Year**



**Table III-2: Number of Genetic Counseling Cases
From Imperial County by Year**

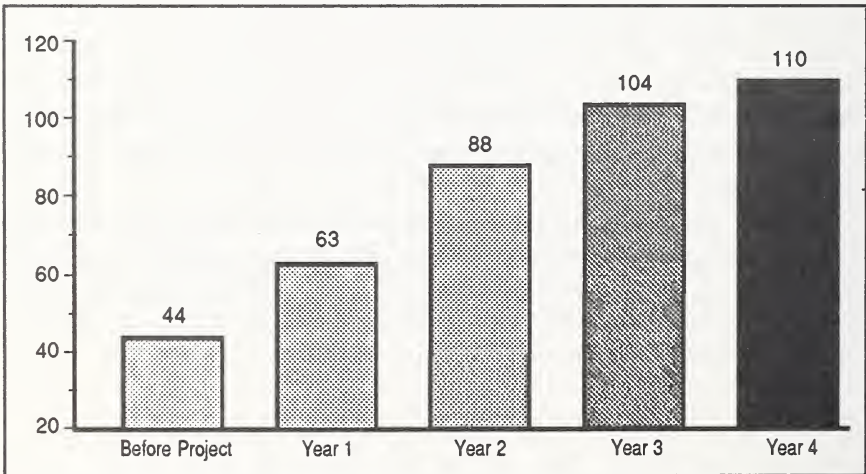


Table III-3:
Ethnicity of Clients by Year

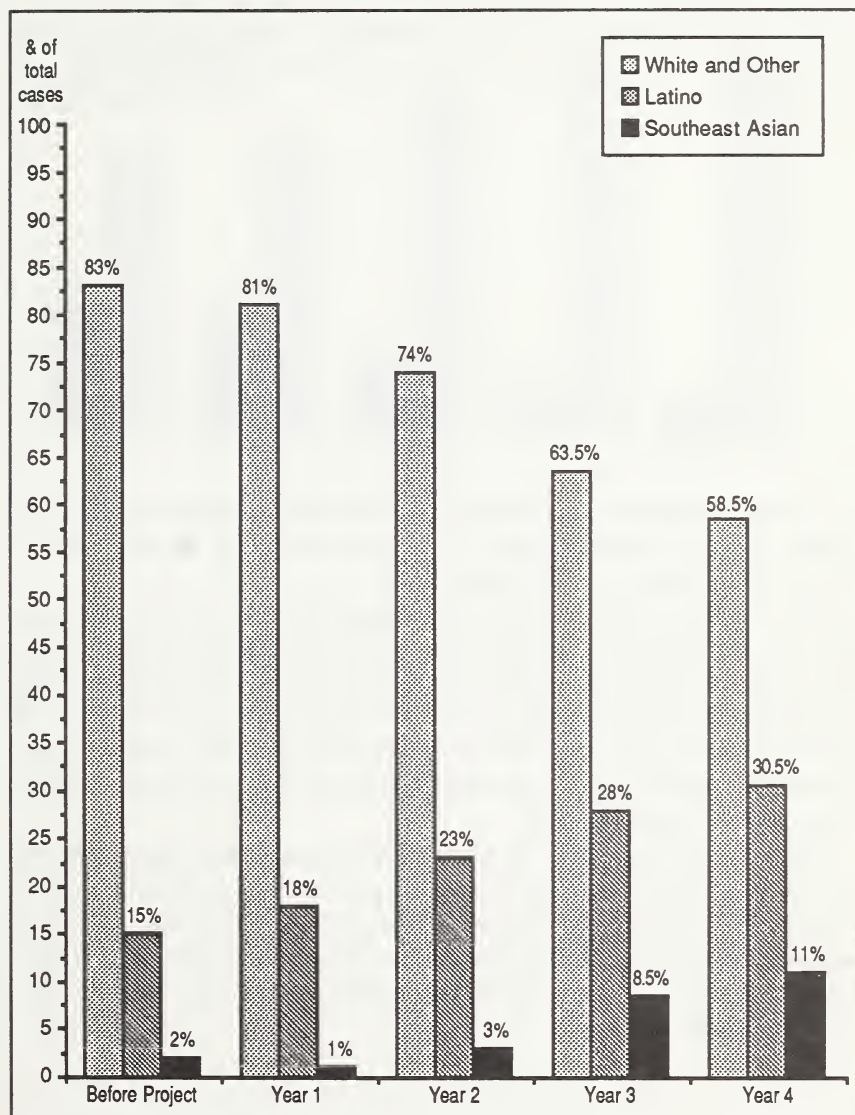
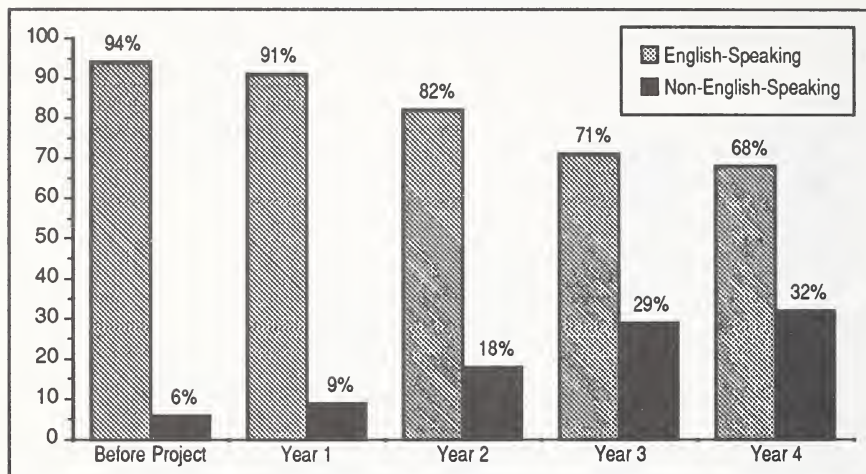


Table III-4: Percent of Non-English-Speaking Clients by Year

Looking at the ethnic composition of the total cases served by year, the percentage of Latino clients increased by more than 200% and the percentage of Asian clients increased by 550% (table III-3).

The absolute number of English-speaking clients stayed about the same. However, that number as a percentage of the total dropped by 26% (table III-4). The number of non-English-speaking clients rose from 34 (28 Spanish-speaking, 6 Southeast Asian) before the project to a total of 242 (177 Spanish, 65 Southeast Asian) by the end of the fourth year. These numbers represent an astonishing increase of 530% in non-English-speaking clients, who now comprise about one third of our caseload.

These dramatic changes in the geographic location, ethnic composition, and primary languages of the clients served during a relatively short period of time, document the importance of employing bilingual/bicultural genetic counseling assistants whenever possible, even if they must be trained "on the job." The importance of having the capability to provide outreach to these populations cannot be overemphasized.

This project demonstrates that individuals/families in geographically isolated areas, as well as those of Latino and Southeast Asian descent, are receptive to and will utilize genetic counseling information and services when such information and services are made accessible to them. As a result of this project, two new genetic counseling positions have been added to the San Diego Regional Center for the Developmentally Disabled, and service to these populations continues.

Recommendations

CONSENSUS RECOMMENDATIONS

ETHNOCULTURAL CONSIDERATIONS

Statement of the Problem

Underserved populations exist because of a multitude of barriers in our society. These barriers include poverty, language, ethnocultural differences, geographic isolation, multiple disabilities, and religious/philosophical differences.

The barriers caused by poverty can only be broken down by making full health care available in a sensitive manner to all. The delivery of genetic services is significant, but it only accounts for a portion of the medical care required for the truly needy.

Communication barriers, raised due to language differences, are common in our country with its rich mixture of Hispanics, Southeast Asians, and other immigrants. This serious problem cannot be solved by just using translators, but necessitates the training and employment of understanding, sensitive interpreters. Bilingual or native language care would be preferable, and efforts should be made to train minorities as professionals in genetics. Some languages used in the U.S. today do not even have a genetics vocabulary!

Ethnocultural differences are perhaps the greatest barrier to receiving care. Most caregivers are ignorant of the differences which exist between peoples whose philosophy, life experience, values, and history vary and are often unknown or misunderstood. The feelings, emotions, and desires of others are probably similar from culture to culture, but their expression can be quite different. The ability to interpret nonverbal language and to understand the social pressures or the role of gender from one society to another may blind the genetic caregiver to the psychosocial needs of his or her client.

Service providers who care for different cultural/ethnic groups must make every effort to learn about important practices and beliefs of the people they wish to serve and to become sensitive to the effect of the help they wish to give.

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Professionals must learn from consumers about the effects of their service and grow to understand and respect the societal differences.

Religious/philosophical differences are often a barrier at the care level. Understanding the basic value system of a community is essential. For example, if the patient is Buddhist, understanding the basic tenets of Buddhism is necessary, but it is also important to realize that the interpretation of the teachings may vary among groups of Buddhists. Health professionals must learn about their community's orthodoxy and interpretation without stereotyping. This recommendation holds for all the religious/philosophical systems embraced by consumers of services. Health professionals should contact the local clergy, as the clergy at times are unaware or even suspicious of the genetic care provider, but can frequently benefit from an opportunity to learn about genetics and therefore counsel and comfort his or her people more effectively.

Consumers too have a role to play. The role of health professionals should not be paternalistic, but both consumers and professionals should share the responsibility for overcoming ethnocultural barriers to genetic services.

Strategies and Recommendations

- Provide adequate health care regardless of ability to pay.
- Train interpreters; do not just use translators.
- Recruit minority genetic care professionals.
- Learn the culture of those you serve, their nonverbal language, their social values, and their view of family.
- Learn the basic philosophy and religious beliefs of your client.
- Learn what your client wishes and needs to know in order to give the best care to his or her family.
- Do not stereotype everyone who claims the same philosophy/religion; regional and local orthodoxy and interpretation may vary widely.
- Inform and educate clergy or spiritual care people so they may effectively comfort and counsel their people.

ECONOMIC AND INSURANCE CONSIDERATIONS

Statement of the Problem

Over the past three decades, medical genetic services have been developed and provided primarily through academic medical centers and state health departments. Funding for genetic services has involved a wide variety of mechanisms: state, federal, and private foundation grants for service; research grants; reimbursement from private and public (third-party) insurance programs; unreimbursed consumer payments; and subsidization by other medical services (i.e., "free" care in academic centers). Although the mix of payment sources has fluctuated over the years, currently the financial stresses on the system that provides genetic services are more severe than ever. The stresses are being felt by providers, consumers, and third-party payers.

From the provider perspective, non-procedural services (e.g., genetic diagnosis and counseling) are labor-intensive and extremely time consuming. Providers have been slow to optimize their clinical practice income. Providers could benefit from the utilization of the current procedural terminology (CPT) codes, which are approved by the American Medical Association and accepted by third-party payers. Currently, new codes need to be developed to address the needs of underserved populations. The cost of providing services to underserved populations is relatively much higher than the cost of providing services to the general population, and reimbursement is proportionately less. Present reimbursement programs do not pay for nonphysician services, such as interpreters for the deaf and hearing impaired, or for non-English-speaking clients. Additionally, the cost of drug therapies for genetic disorders is generally not covered, and it is particularly difficult to get coverage for treatments which are past the research stage but not yet considered accepted practice.

From the consumer perspective, lack of health insurance is a major problem. Unfortunately, no comprehensive studies have addressed this issue. It is clear that some people are denied insurance, have pre-existing conditions excluded, or are restricted in changing employment because of hereditary disorders. Furthermore, health insurance programs are often complex, are constantly changing, and are placing more of the burden of accessing benefits on the consumers. Consumer knowledge is grossly inadequate for identifying, success-

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fully applying for, and utilizing health, life, and disability programs. Often reimbursement is based on a "usual and customary" charge, which may be much less than the actual charge. Other financial burdens include the cost of traveling to widely spaced genetic centers and the potential loss of insurance for medical care when a child reaches age 21 and is no longer eligible for services provided to children with special health care needs, or is no longer a student and covered by parental insurance policies. Finally, few studies have addressed the cost of hereditary disorders, both the obvious medical and insurance expenses and the not-so-obvious expenses of time lost from work, child-care, and so forth.

Although third-party health insurers were not present at this symposium to represent the full scope of their problems, some points seem clear. First, the private marketplace is highly competitive and reduction in expenses is a prime goal. Second, public insurance programs (e.g., medical assistance and Medicare) are being curtailed, often severely. Third, consumer groups which are effective in lobbying for expanded service coverage have been less aggressive recently, and are generally uneducated about the importance of genetic services. Fourth, insurers do not recognize the significance of genetic services, because specific CPT codes have not been developed and accepted, and medical genetics is not widely or officially recognized as a medical specialty.

Strategies and Recommendations

- Mechanisms must be found for faculty to devote time to nonprocedural clinical activities that are not financially self-supporting if academic medical centers are to remain major providers of genetic services.
- Attention must be paid to the declining number of physicians who are entering the clinical genetics field.
- Mechanisms for enabling nonphysician providers of genetic services (counselors, nurses, social workers, etc.) to charge for and be reimbursed for their efforts need to be developed.
- Clinical geneticists need to be educated about how to optimize charges and collections within the presently flawed system.

- The current national effort to revise CPT codes to reflect more accurately nonprocedural genetic services must continue and receive support from a broad coalition of providers and consumers.
- International Classification of Diseases (ICD) codes must be revised for hereditary conditions. Their routine use on discharge summaries and other diagnosis reporting forms must be encouraged in order to establish accurate data bases. The Centers for Disease Control (CDC) and the Council of Regional Networks for Genetic Services (CORN) are working on this.
- Consumers need to be educated about the range of insurance options available to them for health, disability, and life coverage. This is done most effectively, but at substantial cost in labor and time, by individual counseling. Support groups might provide this counseling as a service to its members.
- Administrators of insurance programs need to be educated about genetic services because genetic services can actually reduce costs in the long run and serve as preventive health measures. They also need to be informed about the natural history and prognosis of those diagnosed with genetic disorders.

A range of investigations must be encouraged and supported:

- To determine the true financial costs of various hereditary disorders to consumers;
- To determine the scope of insurance coverage acquired by people with hereditary disorders, the costs of coverage, the types of ratings, exclusions and waiting periods, and all unmet needs;
- To determine the costs of providing genetic services, how well they are reimbursed, and whether services can be delivered more cost-effectively;
- To document insurance company criteria for rejecting coverage, rating subscribers, and enforcing exclusions of diagnoses; and
- To document local criteria for determining disability eligibility.

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Various legislative and policy initiatives need aggressive support:

- Revision of Social Security Insurance (SSI) criteria to include educational, vocational, and children's programs, such as proposed by HR 868;
- Working toward a sensible, equitable, less expensive system of allocating and paying for medical services;
- Expansion of state and federal support of genetic services, especially for populations which are currently underserved;
- Provision of continuity of insurance coverage from programs targeted to children and adolescents to programs which also cover adults;
- Promotion of national health insurance without discrimination against people with hereditary disorders;
- Revision of physician payment systems. The resource-based relative value scale (RBRVS) model is worth a trial; and
- As the range and availability of laboratory tests of genetic susceptibilities (e.g., DNA screening) expands, careful attention must be paid to potential discriminatory applications in limiting access to all types of insurance.

COORDINATION OF SERVICES TO UNDERSERVED POPULATIONS

Statement of the Problem

Delivering genetic services to underserved populations is hampered by a lack of coordination. Specifically, access to data is limited, referral networks are underdeveloped and underutilized, and health care providers need to develop holistic approaches that integrate the physical, spiritual, cultural, and psychological needs of consumers and their families.

Strategies and Recommendations

- Strengthen the mandate on both state and federal levels for the collection and analysis of data/needs assessments for genetic services.
- Encourage active dialogue between voluntary genetic health organizations and genetic and public health professionals in support for and use of statistical reporting of genetic needs and services.
- Encourage state and federal governments to expand financial support for the various systems of genetic data collection, including the Council of Regional Networks for Genetic Services (CORN), Centers for Disease Control (CDC), birth defects registries, the National Center for Health Statistics, and National Institutes of Health (NIH).
- Have the consumer committee from each regional genetic network develop a comprehensive listing of all disease-oriented network groups (both professional and consumer) and have this information available for families and professionals.
- Train professionals about networks and the role of parents in the treatment process and make continuing education in this area mandatory.
- Contact resource organizations, such as city and state listings, the Federal Registry Listing, March of Dimes Birth Defects Foundation, United Way Foundation, churches, the Foundation Center Network (1-800-424-9836), etc.
- Advocate delivery of services by a multidisciplinary team that would include clients, parents, physicians, nurses, genetic counselors, social workers, spiritual advisors, and other support service personnel when necessary. Referral of clients and families to support groups would be one of the team's activities.
- Advocate educational activities by the team to raise awareness among consumers and professionals who render services to the client and family.
- Encourage the identification and exchange of resources by the genetic and adoption committees from various organizations such as the Alliance of Genetic Support Groups, CORN, the regional networks, and

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the national adoption networks. Encourage the development of a consumer support network for special needs adoption families, especially those with children who have genetic conditions.

- Encourage the identification and exchange of resources by the genetics and adoptions committees, such as the Alliance of Genetic Support Groups, CORN, the regional networks, and the national adoption networks. Encourage the development of a consumer support network for special needs adoption families (especially genetic conditions).

EDUCATION

Statement of the Problem

There is a need for education in genetics on all levels. Potential consumers should be targeted in our schools and through the media. Education on genetic services demands a closer relationship between professionals and consumers.

Strategies and Recommendations

- All children should have the benefit of genetics education (as well as the study of biology) from kindergarten through twelfth grade. Curricula that have been developed need to be implemented more widely and must be updated to reflect technological advances and expanded to include a more humanistic and sensitive approach to the presentation of genetic disorders. School administrators should be encouraged to incorporate genetics curricula into the school program.
- The general public must be better informed about genetic services, and should focus on the successes and accomplishments of individuals with special needs in our society. The media should be utilized to make society more aware of genetic disorders.
- Consumers and professionals need to educate themselves about utilizing the media. They must network and share materials, develop new and appropriate materials for specific target audiences, and educate the media on the public need for genetic services.

- Professionals and consumers must work together to address the educational needs of their communities.
- Parents of children with special health needs, children, and adults with disabilities should have input in the teaching of health professionals.
- There should be a federal mandate for training of persons within underserved groups to establish a partnership between health care professionals and consumers.
- Cross-cultural training should be offered within accredited courses and continuing education programs for genetics professionals.
- Professionals should make themselves available as resources to consumer support groups and educate support personnel in lay terms. In particular, professional education needs to include sensitivity training for health care professionals.
- There is a tremendous need for professionals from minority and cross-cultural backgrounds to be trained and placed in the field. We must start early in the educational system to draw minorities into genetics professional education with innovative strategies and incentives. Examples include agency-sponsored scholarships and special programs to train parents of affected children.
- Funding must be available to help students overcome the financial barriers to professional education.

LIFE CYCLE CONSIDERATIONS

Statement of the Problem

Designs for the provision of genetic services have been preoccupied by childhood models. In our education, health care structure, and insurance arrangements, we have not provided adequately for transition to adult life. Further, the adult with disability is not adequately incorporated in the establishment of attitudes and policies. Parents and involved adults have much to teach, including in the area of the values surrounding prenatal counseling. The involved ado-

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lescent and young adult deserve more thoughtful consideration in the adaptations made for services.

Strategies and Recommendations

- Genetic support services should achieve continuity from birth through adulthood, with particular attention to transition from childhood. This has a mandate for programs in centers and in the planning of departments of health. It is also pertinent to the content of professional education.
- Advice from children and adults who themselves have disabilities and who are the ultimate experts on service requirements should be recognized. Parents and involved adults have particular insights for training professionals in the issues surrounding prenatal diagnosis counseling and in supporting families being counseled.
- Services provided to adolescents and young adults must acknowledge their special needs and growing maturity. Conventional design should be modified to accommodate their available time, their social style, and their requirement for self-determination.
- Individuals with late onset disorders (genetic disorders which are not expressed until late in the life cycle), particularly adults, need to be recognized and should have funding and services provided to them.
- Financial assistance for testing and screening costs should be available for individuals at risk for genetic disorders.
- Eventually disorders such as hypertension, asthma, and schizophrenia, which are now thought to result from the interaction of environmental factors and heritable factors, will be classified as genetic disorders.

CONSUMER EMPOWERMENT

Statement of the Problem

There is a missing link between health care professionals and many of the populations for whom they do or should provide services. Differences in ethno-cultural backgrounds can generate misinformation and mistrust between professionals and their clients. There is inadequate recognition of the importance of families in policy formation. Consumers' roles as advocates are vital.

Strategies and Recommendations

- Providers and planners should improve relations with minority communities by working with local leaders to make available information about possible genetic service needs and the existing programs.
- Programs should be created to facilitate the development of self-advocacy. There should be a national commitment for the formation of consumer support groups, including those within ethnic or cultural associations; their potential for advocacy is of critical value. Professional assistance should be given freely to help consumers help themselves.
- Parents of children with special health needs, and children and adults with disabilities, should have input in every phase of the delivery of services, including client conferences and policy formation. Often this may involve incentives and supports, such as travel funds, educational opportunities, and program participation.
- A consumer concerns committee should be active in each regional genetic service network. The committee should provide pertinent information for families and professionals, and assist in referrals.
- A committee should be developed that examines and evaluates terminology with consumer input to avoid the use of negative language in describing disorders and persons with genetic disorders. Additionally, as commonly used terms become pejorative (e.g., handicapped or disabled), the committee should modify the terms to ones that are more acceptable (e.g., physically challenged).

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- Informed consumers should participate in the development, approval, implementation, and evaluation of research protocols and activities to insure that the research is responsive to consumer problems.
- A consumer advisory committee with a reporting function should be required in all Requests for Proposals (RFPs) to ensure that "community empowerment" and "consumer empowerment" are not theoretical statements made by providers, but are applied practices.

GEOGRAPHIC CONSIDERATIONS

Statement of the Problem

Accessibility to genetic services is affected by wide geographic dispersion of populations. This leads to community isolation and limited access to medical services.

Strategies and Recommendations

Geographic barriers are surmountable only with greater flexibility on the part of professionals to reach out to the small cities and towns, and to the local, state, and federal governments to provide funds for transportation, when necessary, to those who need care at genetic service centers. Eventually some geographic barriers may be overcome by providing genetics education and counseling using the versatility of the electronic media.

To improve availability of genetic services to these geographically isolated populations, it is necessary to:

- Conduct local needs assessments to define the community plan and identify specific cultural needs;
- Establish satellite clinics which utilize local resources and regional medical genetic centers;
- Demand adequate financial support to provide transportation needs and bilingual staffing needs;
- Develop and expand unique educational initiatives for consumers;

- Utilize local resources to develop self-help strategies to address unmet needs of families;
- Remove artificial boundaries to treatment centers created by locating treatment centers in regions that are not accessible to all individuals;
- Provide transportation or financial assistance for transportation; and
- Access special resources, such as the Air National Guard, which in special cases can provide air transport to distant medical clinics.

LEGISLATION

Statement of the Problem

The barriers that impede or prevent effective legislative actions relate, in large measure, to a lack of understanding of genetic problems by legislators, policy makers, and the public. There is a general lack of understanding about genetic problems. Because many do not understand that everyone is at risk for genetic disorders, there is inadequate constituent or voter interest and support, and insufficient money to meet current and future needs of individuals and families with or at risk for genetic disorders. These resources for genetic services have created increased competition for funds while at the same time responsibilities have been increasingly shifted to the states. This has created diffusion and variation of programs in states and causes a greater inequality of access to care. In addition, the shift of responsibility to the states makes accountability more difficult.

Strategies and Recommendations

- Educate the general public, schools, policy makers, and support groups/coalitions about legislative issues and the legislative process.
- Strengthen and enhance existing coalitions/networks.
- Urge genetic service providers and consumers to continue working with coalitions such as the National Organization for Rare Disorders (NORD) and the Alliance of Genetic Support Groups to speak with a

united and powerful voice, and to reject the myth that there cannot be sufficient resources for those in need.

- Urge coalitions to accept the responsibility for educating their membership organizations so that their political effectiveness may increase as they continue with personal testimony and expert documentation.
- Switch to consumer empowerment.
- Increase legislative efforts on the grassroots level.
- Restore federal direction of the MCH Block Grant.
- Reauthorize funding for newborn screening and follow-up.
- Support legislation to increase funding for biomedical research and the MCH Block Grants.
- Support current legislation in which the U.S. Department of Health and Human Services is collecting data from all states on adoptions, and recommend that the regulations include specific data identification about genetic conditions. (Contact person: Mary Beth Seader, National Committee for Adoption, 1930 17th Street, N.W., Washington, DC 20009, (202) 328-1208).
- Support legislation to maximize opportunities for reimbursement of health care costs for children with genetic conditions who are adopted through any adoption mechanism. Include the adoption population in other deliberations of health care reimbursement issues for genetic conditions.

WORKSHOP RECOMMENDATIONS

THEME I: SCOPE OF THE PROBLEM

RELIGIOUS ATTITUDES AND THEIR EFFECT ON THE PROVISION OF GENETIC SERVICES

Statement of the Problem

- Religions of the world interpret reality as defined by God through revelation, and for individuals or institutions to change parts of that reality is threatening to the total meaning.
- Often health care providers neither understand the religion of their clients in its ideal formulation nor understand how the local group interprets the ideal in the local situation.
- Clergy are not always aware of the science of genetics or the effects of genetic decisions made by their people.

Strategies and Recommendations

- Have health care professionals understand the roots of beliefs of the populations they are trying to serve.
- Have health care professionals recognize local differences among those who practice a religion and avoid stereotyping.
- Understand barriers to clergy education and overcome those barriers to provide adequate education to the clergy.

GEOGRAPHIC CONSIDERATIONS WHICH AFFECT ACCESS TO GENETIC SERVICES

Statement of the Problem

- Geographic, economic, and cultural barriers prevent access to genetic services.

Strategies and Recommendations

- Identify existing resources and ways to increase/improve resources.
- Form coalitions to work together.
- Seek financial assistance for transportation to institutions that provide genetic services.

COMMUNICATION BARRIERS WHICH LIMIT ACCESS TO GENETIC SERVICES

Statement of the Problem

- The scarcity of qualified interpreters, lack of cross-cultural understanding, and lack of effective consumer education materials contribute to inadequate access to care.

Strategies and Recommendations

- Train qualified interpreters in the specific needs of genetic counseling communication.
- Make medical providers aware of their responsibilities in securing qualified interpreters and working with them most effectively.
- Sensitize providers to the importance of specific cultural characteristics; for example, nonverbal behavior, gender roles, family structure, and religious beliefs.
- Develop client education materials to meet needs of specific populations, including the development of a genetic vocabulary for those languages which lack this vocabulary and the associated concepts.

THE EFFECTS OF ETHNOCULTURAL BACKGROUND ON ACCESS TO AND USE OF GENETIC SERVICES

Statement of the Problem

- Current provision of genetic services lacks sensitivity, understanding, and acceptance of ethnocultural values of the populations served. This includes many institutional policies.
- Current provision of genetic services needs to develop different models of intervention based on client needs.
- Language gaps can create misunderstandings arising from differences in cultural values and communications (cultural and class stereotypes).
- Clients distrust the health care system due to repeated negative experiences.
- High medical costs inhibit potential clients from seeking medical attention (approximately 25 percent of the population lacks health insurance).

Strategies and Recommendations

- Urge providers to work at understanding their community values.
- Empower communities by working with community leaders.
- Educate providers and students about self-awareness.
- Collect data on how groups are using services.
- Understand the epidemiology of diseases among specific groups.
- Encourage greater representation and recruitment of minorities into genetic/health professions.
- Solicit participation of groups and "payers" (federal, state, and third-party) in the planning of genetic services/programs.
- Work with existing providers in communities.

NEEDS ASSESSMENT: IDENTIFYING THE UNDERSERVED

Statement of the Problem

Identification of the underserved is hampered by:

- Few statistics describing genetic diseases and services;
- Lack of a policy imperative to gather and analyze information;
- Lack of federal/regional/state coordination in the collection and analysis of information;
- Lack of access to certain data that may be available from private insurance institutions.
- Lack of diagnostic tools/classifications.

Strategies and Recommendations

- Strengthen the mandate on both state and federal levels for the collection and analysis of data/needs assessments for genetic services.
- Encourage active dialogue between voluntary genetic health organizations and genetic and public health professionals in the support for and use of statistical reporting of genetic needs and services.
- Encourage state and federal governments to expand financial support for various systems of genetic data collection, including the Council of Regional Networks for Genetic Services (CORN), Centers for Disease Control (CDC), birth defects registries, the National Center for Health Statistics, and the National Institutes of Health (NIH).

**ECONOMIC BARRIERS
FROM THE CONSUMER PERSPECTIVE**

Statement of the Problem

- It is difficult for consumers to obtain and retain insurance.
- Lack of transportation and need of an aide serve as barriers for consumers.

Strategies and Recommendations

- Use state and federal resources, such as state commissioners of insurance and Departments and Bureaus of Maternal and Child Health, for assistance in procuring insurance.
- Educate consumers about obtaining insurance. Individuals with special health needs should seek out "insured" jobs, such as public service, government agencies, and large companies.
- Join support groups to advocate or form a group of your own for policy facilitation (ethnic or cultural associations).
- Identify alternative payment methods, such as public assistance, sliding fee scale, or becoming involved with a research project.
- Form a clearinghouse for research protocols.

**ECONOMIC BARRIERS
FROM THE PROVIDER PERSPECTIVE**

Statement of the Problem

- Nonprocedural genetic services are labor intensive and poorly reimbursed.
- The cost of providing genetic services to underserved populations is relatively more, and reimbursement is proportionately less, than providing the same service to other populations.
- Present reimbursement schemes do not include provisions to reimburse for nonphysician genetic professionals' time and/or skills.
- A wide diversity in state support for genetic services perpetuates unequal access to care.

Strategies and Recommendations

- Revise CPT codes to adequately reflect the labor-intensive activities performed by genetics professionals.
- Work toward the inclusion of all genetic services as covered policy benefits in both private and public insurance policies.

262 Recommendations

- Support the current initiative to revise physician payment by means of a resource-based relative value scale (RBRVS).
- Sponsor further national studies of reimbursement problems.
- Continue and expand federal and state support of genetic programs.
- Encourage all national organizations including, the Association of Cytogenetics Technologists (ACT), the Alliance of Genetic Support Groups, the American Society of Human Genetics (ASHG), the Council of Regional Networks for Genetic Services (CORN), the American Board of Medical Genetics (ABMG), the International Society of Nurses in Genetics (ISNG), the March of Dimes Birth Defects Foundation, and the National Society of Genetic Counselors (NSGC), who are involved in and concerned with the economic aspects of genetic services to work closely together.

SOCIETAL VIEW OF GENETIC DISORDERS

Statement of the Problem

- There is a lack of culturally sensitive services available.
- Existing myths persist regarding genetic disorders.

Strategies and Recommendations

- Create self-help support groups and referral networks.
- Provide multilingual/multicultural education of the public and health providers regarding genetic disorders.
- Encourage government (local and federal) commitment to funding/services.
- Develop a professional/client rapport based on patience, trust, and love.

CHANGES IN ACCESS FROM BIRTH TO ADULTHOOD

Statement of the Problem

- There is fragmentation and a lack of coordination and continuity of genetic services and genetic support services for families and individuals, both children and adults, who are impacted by birth defects.
- There is also a lack of affordable insurance due to the termination of federal and state programs as individuals reach adulthood.

Strategies and Recommendations

- Medical training and education should be more comprehensive for those in the health field and for parents in order to provide appropriate genetic support services from birth to adulthood for individuals with birth defects.
- Medical professionals dealing with children with special health needs need to network when the transition is being made to adult services.
- The Department of Health must recognize that birth defects do not end at age 21. They must facilitate continued care of the adult with birth defects.
- Legislative action must be taken at the state level to make affordable medical coverage available.

CONSIDERATIONS OF THE DISABLED

Statement of the Problem

- Changing needs of the individual and family are not being appropriately addressed, such as the need for role models and the ongoing need for medical/genetic/social services as life cycle events occur.

Strategies and Recommendations

- Medical and genetics care for individuals with special health needs should be continuous for their entire life span, and medical education should prepare health professionals for treating individuals with chronic illnesses for their entire life span.

264 Recommendations

- Parents of children with special health needs, children, and adults with disabilities should have input in every phase of the delivery of services, including policy formation and in the preparation of education materials on the psychosocial aspects of genetic disorders.

Theme II: Barriers to Care

LACK OF REFERRAL NETWORKS

Statement of the Problem

- There are not enough networks.
- There is not enough information available about established networks.
- Established networks are not used adequately.
- There is no plan for continued nurturing and development of networks.
- There is no national network information line to cover all established networks.
- Professionals are unaware of existing networks and therefore do not use networks to their clients' advantage.

Strategies and Recommendations

- Have the consumer committee from each regional genetic network develop a comprehensive listing of all disease-oriented network groups (both professional and consumer), and make information available to families and professionals.
- Train professionals about networks and the role of parents in the treatment process, and make continuing education in this area mandatory. Include curriculum development in graduate professional schools and professional societies.
- Disseminate information about the accessibility of existing networks and success stories about the work done through networks to the press and medical journals.
- Have networks form liaisons with major medical providers, other disability networks, chambers of commerce, legislative bodies, and any group that can assist them in program development and funding.

SOCIAL STIGMA: HOW IT AFFECTS THE INDIVIDUAL AND THE FAMILY

Statement of the Problem

- Social stigma is difficult to define. (Goffman defines stigma as an attribute, an undesired differentness, that discredits or disqualifies the individual from full social acceptance.)
- There are many causal factors linked to social stigma (terminology, economic, language).
- Labeling exists.
- Cultural myths about drugs, illnesses, causal mechanisms (etiology), morals, karma, curses, and fate persist.
- Medical myths, for example, a sickle cell client's request for pain relief improperly regarded as drug-seeking behavior, continue.
- Provider and consumer ignorance continue.

Strategies and Recommendations

- Consumers with special health needs should help educate health professionals.
- Involve professionals and consumers in policy development.
- Develop positive role models.
- Eliminate labeling.
- Use the media to mold public opinion and show positive aspects of the whole person.

PROBLEMS ASSOCIATED WITH ADOLESCENTS RECEIVING GENETIC SERVICES

Statement of the Problem

- The treatment of genetic disorders interferes, sometimes unnecessarily, with important adolescent needs and activities, especially school, after-school activities, and social relationships.

- Adolescents with genetic disorders find that knowledge of their disorders and associated treatments are not always acknowledged, heard, and/or considered by health professionals or their own families.
- Most teenagers do not want to be considered as being different; they do not want to be labeled or treated as a problem, but as a person.

Strategies and Recommendations

- Institute evening and weekend hours for clinic appointments.
- Encourage health professionals to recognize the value of listening to the expertise of the adolescent. They need to be cognizant of the special problems of adolescents. Health professionals might benefit from listening to a group of adolescents, some with and some without genetic disorders, so each point of view can be seen and their differences and similarities can be recognized.
- Support groups should offer fun things to do, like games, trips, and other activities that teenagers like to do and talk about, instead of focusing entirely on the disorder process. The public needs to become more responsive to the needs of adolescents with special health needs.

ADOPTION OF CHILDREN WITH GENETIC DISORDERS

Statement of the Problem

- Children in foster care with genetic conditions are not properly identified and, even if identified, statistics are not maintained about them.
- Adoption workers and potential adoptive families lack knowledge about genetic conditions and resources. There is a need for pre- and post-adoption services to support placement of children with genetic disorders.
- It is difficult to acquire funding for health care support for adopting children with genetic conditions, and a concern remains about the unavailability of Medicaid and subsidized adoptions in specific cases.

Strategies and Recommendations

- Encourage the identification and exchange of resources by the genetics and adoptions committees (e.g., Alliance of Genetic Support Groups, the Council of Regional Networks for Genetic Services [CORN], the regional networks, and the national adoption networks).
- Encourage the development of a consumer support network for special needs adoption families, especially those with children who have genetic conditions.
- Support current legislation in which the Department of Health and Human Services is collecting data from all states on adoptions. Find out if the regulations include specific data identification about genetic conditions. (Contact person: Mary Beth Seader, National Committee for Adoption, 1930 17th Street, N.W., Washington, DC 20009. 202/328-1208.)
- Support legislation to maximize opportunities for reimbursement of health care costs for children with genetic conditions who are adopted. Include the adoption population in other deliberations of health care reimbursement issues for genetic conditions.

PROVISION OF SERVICES TO ISOLATED POPULATIONS

Statement of the Problem

- Accessibility to genetic services is affected by the problem of wide geographic dispersion of populations, which leads to community isolation and limited medical services. This problem is directly related to the lack of financial resources in states with wide geographic population distribution and inadequate commitment to health care needs.

Strategies and Recommendations

- Increase ability for identification of the needs of populations, incorporating an awareness of cultural attitudes.
- Expand unique educational initiatives.
- Incorporate genetic services into existing outreach efforts.

- Encourage state legislatures and other funding sources to provide funds for expansion (or initiation) of genetic outreach services through the involvement of consumer groups.
- Set priorities based on client care needs rather than on more traditional descriptive diagnostic services.

FINANCE/INSURANCE ISSUES

Statement of the Problem

- Claims are based on "reasonable and customary" costs.
- There is insufficient provider education.
- Some services may not conform to existing system guidelines.
- Payment systems are complex and are difficult to access.
- Coding systems for reimbursement are inadequate or inappropriate for genetic services.
- Genetic services are not part of the standard package offered by many health maintenance organizations (HMOs).
- There is a lack of client involvement in claim submission.
- Genetic services are not clearly defined as important components of comprehensive health care.
- Referrals are usually made from advocacy groups instead of health professionals.
- Guidelines for genetic services need to be developed.

Strategies and Recommendations

- Geneticists need to have more incentives to see clients.
- Geneticists need to be more visible and organized.
- Geneticists and advocacy groups should form a coalition.
- Genetic services must be clearly defined as a significant component of comprehensive health care.

270 Recommendations

- Both providers and underserved consumers need to be educated about finance and insurance issues.
- Use of Medicaid and other assistance needs to be increased.
- Use of nonphysician genetic service providers needs to be increased.
- A master's degree or a board certification should be required for genetic providers.
- Support groups should be encouraged to use financial assistance counseling.

SPECIAL PROBLEMS OF RECENT IMMIGRANTS

Statement of the Problem

- Difficulties in communicating inhibit the provision of care.
- There is a lack of sufficient understanding due to language barriers. This is particularly important because many languages do not have words for expressing genetics terminology.
- There is a lack of familiarity with health care systems.
- Services provided are time consuming due to the effort of overcoming communication difficulties.
- It is difficult to understand the rationale behind procedures, techniques, and information required in counseling sessions (e.g., family medical history) due to cultural differences in values.
- Economic difficulties, including lack of health insurance and lack of information about assistance programs, contribute to the problem.

Strategies and Recommendations

- Train bilingual, bicultural providers through: (1) School programs; (2) special training in employment settings; (3) making it an employment requirement and allowing employees to access training; and (4) access (community-based) mass media, including video, print, and radio.

- Educate: (1) Policy makers; (2) program developers; (3) providers (culture, interpersonal skills); (4) school systems; and (5) clients (free training in language, culture, and health care systems).
- Ease financial burdens by: (1) Covering translational costs with insurance; (2) educating clients and helping with access to aid programs; and (3) providing access to care to those without the ability to pay (government subsidy, assistance).

LEGISLATION UPDATE/ AUTHORIZATION AND APPROPRIATION

Statement of the Problem

- Insufficient (inadequate) money has been and is being supplied for meeting the past, current, and future needs of individuals and families with or at risk for genetic disorders.
- The problems and issues surrounding genetic disorders are poorly understood by legislators, policy makers, and the public.
- Policy makers, public, and care providers are insufficiently educated about genetic disorders.
- Constituent (voter) support is needed.
- The coalitions (e.g., Alliance of Genetic Support Groups) are the key to positive change.
- It must be communicated that the whole population is at risk for genetic disorders.

Strategies and Recommendations

- Increase MCH Block Grant dollars for newborn screening, as well as the National Institutes of Health budget.
- Restore federal direction to the MCH Block Grant.
- Strengthen and enhance existing coalitions and networks.
- Educate policy makers, schools, and the public about legislative issues for support groups and coalitions.

MINORITY PARTICIPATION IN SUPPORT GROUPS

Statement of the Problem

- For various social, economic, and cultural reasons, minority groups are hesitant/unable to participate in disease-oriented support groups.

Strategies and Recommendations

- Professionals must have realistic expectations about support groups, accept the transient nature of groups, and realize that clients' needs vary.
- Professionals should act as facilitators, not leaders, and help to identify recruiters.
- Groups should be designed in a culturally sensitive manner.

Theme III: Strategies and Model Programs

CONVERTING CONSUMERS INTO ADVOCATES

Statement of the Problem

- Barriers exist that prevent underserved populations from considering themselves as consumers with rights and therefore making the transformation into consumer advocates.

Strategies and Recommendations

- Support a national commitment or policy to address equal access to health care.
- Create programs to facilitate the development of self advocacy.
- Act to build and develop coalitions of individuals, support groups, providers, etc.

OVERCOMING LANGUAGE BARRIERS

STATEMENT OF THE PROBLEM

- Genetic terminology is often culturally biased (i.e., "normal," "defective," "at risk").
- Translators/interpreters are not given proper training.

Strategies and Recommendations

- Interpreters must be fully bilingual, bicultural, and acceptable to consumers and properly trained by genetic service staff.
- Terms used in genetic counseling should be culturally sensitive, and reviewed by both consumers and professionals when educational materials are developed. Multilingual materials are needed for different literacy levels.
- There should be administrative backing and appropriate funding for interpreters as part of permanent staff.

274 Recommendations

- Providers should receive instruction or training on overcoming ethno-cultural differences and consumers should be educated about genetic services.

PROJECT FUNDING ON LOCAL AND REGIONAL LEVELS

Statement of the Problem

- There is a lack of funds.
- Proposal and grant writing lack specifics.
- There is a lack of knowledge about the availability of resources and organizations that can be instrumental in providing this information as well as the requirements, priorities, and contact person.

Strategies and Recommendations

- Educate legislators about the need for more services.
- Contact resource organizations, such as city and state listings, Federal Registry Listing, March of Dimes Birth Defects Foundation, United Way, churches, and the Foundation Center Network (1-800-424-9836).
- Encourage grant consultation (i.e., making proposal and grant writing creative and innovative). "Make it fit into their (perspective/resource) mold."

OVERCOMING BARRIERS OF INADEQUATE HEALTH INSURANCE

Statement of the Problem

- Currently the U.S. government does not recognize adequate health care as a right. Genetic services need to be clarified and standardized as early services that can save money. Two choices are either accepting or changing the current system.

- Access to health care and coverage for genetic services are denied to many individuals and families due to inadequate health insurance coverage.

Strategies and Recommendations

- To collectively (as consumers and professionals) educate the political structure to the need for comprehensive health coverage, including genetic services, and generate research to demonstrate cost-effectiveness of these services.
- To better access, utilize, and maximize available reimbursement and payment resources.
- Expand existing age-restricted programs (i.e., Children with Special Health Care Needs programs), to recognize and accommodate adult populations.
- Promote and establish a national health insurance which does not discriminate against those with genetic disorders.
- Encourage better coverage for genetic services: (1) Improve definitions of approved procedures; (2) promote coverage as a policy benefit by insurers; and (3) work with medical professionals to assure recognition of genetic services as distinct and necessary medical services.

PROVIDING EDUCATION ABOUT GENETIC SERVICES THROUGH SCHOOL PROGRAMS

Statement of the Problem

- There is a lack of education about genetic disorders, plus a lack of sensitivity to the cultural diversity of U.S. populations.
- Information on genetics in the school/educational curriculum is outdated (e.g., textbooks) and may not include humanistic elements.
- Current genetics education starts too late in school programs.

276 Recommendations

Strategies and Recommendations

- All curriculum materials developed in the area of human genetics should include the humanistic elements, as well as the scientific. Humanistic elements would include information about: (1) The need to safeguard freedom of choice; (2) the positive potential of individuals who have disabling conditions and genetic disorders; (3) sensitivity to cultural diversity; and (4) equal access to education for all.
- Training of all teachers, administrators, and staff is essential and should include the humanistic elements mentioned above.
- Encourage the participation of human resources such as community-based educational groups (e.g., sickle cell programs) and persons with disabling conditions in human genetics education programs.
- Training should include kindergarten through twelfth grade teachers. Student education should start in kindergarten and continue throughout. There should be an effort to collect and review all existing curriculum materials. A model curriculum would be developed using the above guidelines.

LEGISLATIVE ACTIONS (SPONSORED BY THE MARCH OF DIMES BIRTH DEFECTS FOUNDATION)

Statement of the Problem

- Limited resources for genetic services create increased competition for funds.
- Focus has been on influencing federal policy, programs, and legislature while responsibilities have been increasingly shifted to states. Diffusion and variation of programs in states causes more inequality of access and makes accountability more difficult.

Strategies and Recommendations

- Encourage genetic service providers and consumers to continue working with coalitions such as NORD and the Alliance of Genetic Support

Groups, to speak with a united and powerful voice, and to reject the myth that there cannot be sufficient resources for those in need.

- Urge coalitions to take on the responsibility for educating their membership organizations so that their political effectiveness may increase as they continue with personal testimony and expert documentation.
- Increase legislative efforts on the grass roots level, while we insist on improved accountability in the expenditure of Block Grants.

HOLISTIC APPROACHES: HELPING THOSE WITH GENETIC DISORDERS AND THEIR FAMILIES

Statement of the Problem

- Genetic disorders have multifaceted effects; thus, the health care provider needs to identify how the physical, spiritual, cultural, and psychological needs of those with genetic disorders and their families can be met.

Strategies and Recommendations

- Advocate delivery of service by a multidisciplinary team which includes clients, parents, physicians, nurses, genetic counselors, social workers, spiritual advisors, and other support service personnel when necessary. Referral of clients and families to support groups would be one of the team's activities.
- Advocate educational activities by the team to raise the awareness among consumers and other professionals who render services to the client and family.
- Case conferences should include consumer input to evaluate services being designed by the team.
- Professionals should make themselves available to support groups to assist in whatever way the groups deem necessary.

USING THE MEDIA TO PROVIDE PUBLIC EDUCATION ABOUT GENETIC SERVICES

Statement of the Problem

- Existing public education materials are not reaching all potential consumers of genetic services due to cultural, language, literacy, dissemination, and religious barriers.
- There is a significant lack of appropriate educational materials (due in part to inefficient use of existing materials) and use of media.
- Providers and consumers lack knowledge on how: (1) To use media for public education strategies; and (2) to access resources for the development and distribution of public education materials.

Strategies and Recommendations

- Evaluate existing materials and develop new materials for appropriateness (e.g., use of video materials for illiterate populations) in reaching target audiences.
- Promote sharing of educational materials between agencies ("Don't reinvent the wheel"). Encourage networking and sharing among existing organizations.
- Increase knowledge of professional and consumer groups on the use of media and public education.
- Educate the media about public needs and genetic services available to help meet these needs.

RECRUITMENT OF MINORITIES INTO GENETICS-RELATED PROFESSIONS

Statement of the Problem

- Ethnic and racial minorities are under-represented in the fields of genetics and genetic counseling (genetics-related professions).
- A problem throughout the health profession (nursing, medicine) is declining enrollment.

- Entrance requirements and standards for genetic counseling programs serve as financial barriers.
- Entrance requirements for social work programs are also restrictive.
- Some ethnic groups are incorrectly classified (e.g., Cambodians as Asians).
- There are a limited number of points of entry into professions.

Strategies and Recommendations

- Increase the number of scholarships for people in the allied health professions (agency-sponsored, work-related).
- Develop work-related training programs (state-supported).
- Provide incentives and opportunities for advancement in the field (genetics-related).
- Provide training opportunities for parents of children with special health needs (single gene counseling or family advocate, new type of individual).
- Identify persons who are health professionals in the field.
- Begin genetics education early—get mentors for students in junior high school and high school; develop preceptorships.
- Increase public awareness about genetics.

REACHING THE UNDERSERVED THROUGH SUPPORT PERSONNEL

Statement of the Problem

- Support personnel often incorrectly perceive the needs of the underserved.
- There is a gap between health care professionals and the population they serve.

280 Recommendations

Strategies and Recommendations

- Assess the needs of the underserved populations before developing programs.
- Institute a federal mandate for training programs for persons within these groups to establish a partnership between health care professionals and consumers from underserved populations.
- Provide incentives, such as travel funds, salaries, and educational opportunities, to consumers of a variety of ethnocultural backgrounds, to become involved in genetics programs as peer helpers or as coordinators of parent-to-parent programs.
- Provide cross-cultural training in accredited courses and continuing education programs for paraprofessionals.
- Educate support personnel and community leaders, in lay terms, about existing genetics programs.

REACHING GEOGRAPHICALLY ISOLATED POPULATIONS

Statement of the Problem

- It is difficult to reach and serve geographically, culturally, and/or technologically isolated populations.

Strategies and Recommendations

- Base intervention programs on local needs assessments and community plans.
- Establish satellite genetic clinics through collaboration between local agencies and regional medical genetic centers.
- Provide financial support for training and utilization of bilingual/bicultural persons to provide genetic services (consumer advocates/paraprofessionals).
- Identify and utilize local resources to develop self-help strategies to address unmet needs.

Appendices

APPENDIX 1: CONFERENCE PROGRAM

Sunday, May 7, 1989

10:00–12:00 noon **Registration**

12:00–1:30 pm **Lunch/General Session**

Welcome - Rochelle Mayer, Ed.D.

Symposium Director

Mission Statement - Joan O. Weiss, M.S.W.

Honorary Symposium Director

1:45–3:15 pm

Plenary Session,

Theme 1: The Scope of the Problem

Co-Chairs **Robert Baumiller, S.J., Ph.D.**

Deborah Henry

Keynote **James E. Bowman, M.D.**

Speaker *Professor of Pathology and Medicine*

Committee on Genetics

University of Chicago

Plenary **Jane S. Lin-Fu, M.D.**

Responders *Chief, Genetics Services Branch*

Office of Maternal and Child Health

U.S. Public Health Service

F. John Meaney

President, Council of Regional Networks for Genetic Services

Kermit Nash, Ph.D.

*Professor, Chairperson, Health Specialization School
of Social Work
The University of North Carolina
at Chapel Hill*

Glenda Purdie Harris, M.S.A.

*Veterans Administration Medical Center
Sickle Cell Education and Screening Program*

3:30–5:00 pm

Workshops, Theme 1

Religious Attitudes and Their Effect on the Provision of Genetic Services—small group

Geographic Considerations Which Affect Access to Genetic Services—small group

Communication Barriers Which Limit Access to Genetic Services—small group

The Effects of Ethnocultural Background on Access to and Use of Genetic Services—large group

Needs Assessment: Identifying the Underserved—large group

Economic Barriers from the Consumer Perspective—small group

Economic Barriers from the Provider Perspective—large group

Societal View of Genetic Disorders—large group

Changes in Access from Birth to Adulthood—large group

Considerations of the Disabled—small group

In all three Themes, large groups had approximately 40 participants; small groups were limited to approximately 25 participants.

5:15–6:45 pm

Social Hour

Cash Bar, Hors D'Oeuvres

Resource Material Display

Dinner on your Own

Monday, May 8, 1989

8:45–10:15 am

Plenary Session, Theme II: Barriers to Care

Co-Chairs **Marilyn Gaston, M.D.**
Lucy C. Spruill, A.C.S.W.

*Plenary
Speakers* **George C. Cunningham, M.D.**
*Chief, Genetic Disease Branch
California State Department of Health Services*

Ilana Mittman, M.S.
*Genetic Counselor/Project Director
San Francisco General Hospital*

Kate Turnose
The Family Place, Washington, D.C.

Lucy C. Spruill, A.C.S.W.
Disability Advocate

10:30–12:00 noon

Workshops: Theme II

Lack of Referral Networks—large group

**Social Stigma: How It Affects the Individual and the Family—
small group**

**Problems Associated with Adolescents Receiving Genetic
Services—small group**

Adoption of Children with Genetic Disorders—small group

Provision of Services to Isolated Populations—large group

Finance/Insurance Issues—large group

Special Problems of Recent Immigrants—large group

**Legislation Update/Authorization and Appropriation—large
group**

Minority Participation in Support Groups—small group

286 Appendix I: Conference Program

12:00–1:00 pm

Lunch

1:15–2:45 pm

**Plenary Session,
Theme III: Strategies and Model Programs**

Co-Chairs **Allen C. Crocker, M.D.**
Flora Brown

*Plenary
Speakers* **R. Stephen S. Amato, M.D., Ph.D.**
*Director of Medical Genetics
Greater Baltimore Medical Center*

Jane S. Lin-Fu, M.D.
*Chief, Genetics Services Branch
Office of Maternal and Child Health
U.S. Public Health Service*

Beverly Raff, Ph.D.
*Vice President, Professional Education
March of Dimes Birth Defects Foundation*

Desiree Dodson
*Vice President for Consumers
Alliance of Genetic Support Groups*

3:00–4:30 pm

Workshops: Theme III

- Converting Consumers into Advocates—small group
- Overcoming Language Barriers—large group
- Project Funding on Local and Regional Levels—large group
- Overcoming Barriers of Inadequate Health Insurance—small group
- Providing Education About Genetic Services through School Programs—small group
- Legislative Actions (sponsored by MOD)—large group
- Holistic Approaches: Helping Those with Genetic Disorders and Their Families—small group
- Using the Media to Provide Public Education about Genetic Services—large group
- Recruitment of Minorities into Genetics-Related Professions—small group

Reaching the Underserved through Support Personnel—small group

Reaching Geographically Isolated Populations—large group

4:45–7:00 pm

Social Hour

Cash Bar

Resource Material Display

7:00–9:00 pm

Award Banquet

Rochelle Mayer, Symposium Director, presiding

Speakers

The Honorable Robert T. Matsui

*U.S. House of Representatives
(California, Third District)*

Symposium sponsors

APPENDIX 2:

PRESENTERS

Sabree K. Akinyele
R. Stephen Amato, M.D., Ph.D.
Donalda Ammons
Kathleen Shaver Arnos, Ph.D.
Robert C. Baumiller, S.J., Ph.D.
Roxanne Bighorn
James E. Bowman, M.D.
Daniel L. Brant, M.S.W.
Annie Brayboy, M.S.W., M.P.H.
Flora Brown
Augustus C. Brown, Ph.D.
Joan K. Burns, M.S., M.S.S.W.
Jerry Chappell
Chanthan S. Chea
Nuth Chea
Priscilla Ciccariello
Peggy S. Cooper
Allen C. Crocker, M.D.
George C. Cunningham, M.D.
Jessica G. Davis, M.D.
Ven. Maharagama Dhammasiri
Barbara Dixon, R.N., M.N.
Desiree Dodson
Ken Dumars, M.D.
Maria Elena Orrego
Wendy Elliott-Vandivier
Joan Fitzgerald, M.S.
Irene Forsman, M.S.
Legia Freire
Terrie Fritz, M.S.W.
Marilyn Gaston, M.D.
Serina K. Gilbert, A.C.S.W., L.C.S.W.
Evelyn González
Paula K. Haddow, M.A.T.
Erica Hagan
Glenda Purdie Harris, M.S.A.
Anne Harrison-Clark
Deborah D. Henry
Stephanie Henry

Jane A. Leavitt
Lillian S. Lew, M.Ed., R.D.
Jane S. Lin-Fu, M.D.
David Linney
Edward R. B. McCabe, M.D., Ph.D.
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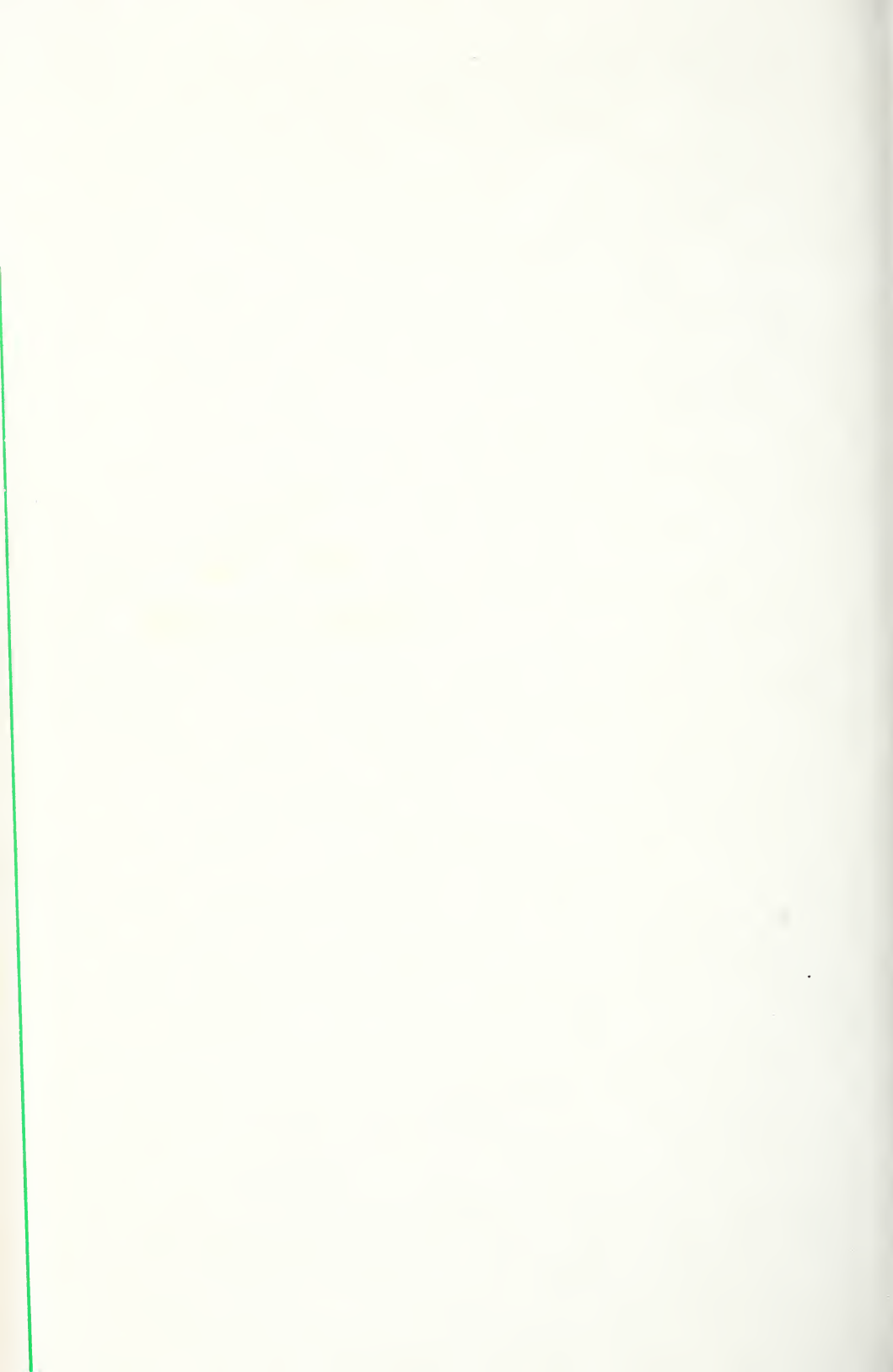
V. 26 no. 3, 1990

STRATEGIES IN GENETIC COUNSELING: REPRODUCTIVE GENETICS & NEW TECHNOLOGIES

Editors: Beth A. Fine
Elizabeth Gettig
Karen Greendale
Bea Leopold
Natalie W. Paul

March of Dimes Birth Defects Foundation
Birth Defects: Original Article Series
Volume 26, Number 3, 1990





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Editors: Beth A. Fine
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Birth Defects: Original Article Series
Volume 26, Number 3, 1990



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Introduction

This was a milestone year for the National Society of Genetic Counselors (NSGC) and the profession of genetic counseling. Ten years have passed since the NSGC was established. Twenty years have passed since the first students entered the first masters degree program designed to train a new allied health professional, the genetic counselor.

From a professional standpoint, numerous developments have occurred. There were eight students in the first graduating class at Sarah Lawrence College in 1969. Today, NSGC membership approaches 1,000. Genetic counselors are employed in most major university medical centers, in the private and public sector, in hospitals, private practice, and in state health departments and in laboratories. Genetic counselors are recognized professionals with a pivotal role in the delivery of genetic services. Their job descriptions have expanded into the areas of patient care, administration, laboratory testing, education, and in public policy.

An important reason for the growth in the genetic counseling profession has been the rapid technologic advancements in molecular genetics and prenatal diagnosis. Therefore, it seemed appropriate that the theme of this year's National Education Conference was "Strategies in Genetic Counseling: Reproductive Genetics and New Technologies." As the NSGC enters its second decade, a look to the future, while considering the past, presents a direction for continued professional enhancement.

The goal of the conference planners was to educate and re-educate ourselves regarding the newest prenatal diagnostic techniques, DNA analysis and its applications, infertility and assisted reproduction technologies. Experts in these areas presented historical perspectives, current data and predictions for the future. Workshops, contributed papers and posters also explored the psychosocial aspects of genetic counseling and prenatal diagnosis, ethnocultural considerations in genetic counseling, genetic counseling methods as well as legal and ethical issues associated with these new technologies.

The first Dr. Beverly R. Rollnick Memorial Lecture in Genetic Counseling was delivered by Kathleen Sulik, PhD, of the University of North Carolina. Her research in embryology and teratology will lead to a finer understanding of craniofacial and other anomalies and to the normal developmental process. Dr. Rollnick, a founding member of the NSGC as well as a specialist in craniofacial genetics, respected the work of Dr. Sulik and we were honored by Dr. Sulik's contribution to this conference.

The 1990 conference marked the first time that the NSGC and the International Society of Nurses in Genetics (ISONG) cooperated in the joint

presentations of contributed papers and posters. We look forward to continued collaboration.

This volume contains selected papers from the proceedings of our conference. We acknowledge the efforts and contributions of all the presenters. In addition, we would like to thank all the members of the Conference Planning Committee for making this high quality meeting possible. Special recognition and appreciation is extended to Virginia Corson and Bea Leopold for their diligence and organizational skills.

We anticipate that the next ten years will be as challenging, productive and rewarding as the last decade.

Beth A. Fine, MS
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Dr. Beverly R. Rollnick Memorial Lecture

Normal and Abnormal Craniofacial Embryogenesis*

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I. INTRODUCTION

An understanding of the normal developmental events occurring in the craniofacial region is necessary to comprehend those changes which result in the malformations that affect this area. It is, therefore, the purpose of the first section of this presentation to review our current knowledge of normal craniofacial embryogenesis and to follow this with consideration of experimentally induced malformations. Most of that which is known concerning both normal and abnormal development has been acquired utilizing animal models. Although mammalian species are receiving increasingly more research attention, much of our information regarding developmental events has been derived from studies of other classes of vertebrates. In many cases, we feel that extrapolation from one class or species to another is appropriate, but in some cases, it leads to misconceptions. Emphasis herein will be placed, wherever possible, on results of studies utilizing mammalian species. Most of the scanning electron micrographs used for illustration and the majority of the experimental data presented are derived from studies of the mouse.

II. NORMAL CRANIOFACIAL EMBRYOGENESIS

A. Gastrulation and Neurulation

The developmental events that precede gastrulation include fertilization and subsequent cleavage of the fertilized egg to form many smaller cells which comprise the morula. Further cell division and formation of a central fluid-filled cavity results in formation of a blastocyst. The cells of the blastocyst that

*Portions of this chapter have been reproduced from Siebert JR, Cohen MM, Jr., Sulik KK, Shaw C and Lemire RJ: "Holoprosencephaly: An Overview and Atlas of Cases." Copyright © 1990 Wiley-Liss, Inc. Reproduced with permission from Wiley-Liss, a division of John Wiley and Sons, Inc.

will form the embryo proper are termed the inner cell mass, with the remaining cells forming supporting tissues. [The reader is referred to embryology texts for a detailed review of these developmental events (eg, Hamilton et al, 1976; Gilbert, 1988).] In the second week postfertilization in the human, the cells of the inner cell mass are aligned as a bilayered disc. The "upper" layer of this disc is termed the epiblast and the "lower" layer is called the hypoblast. The epiblast is in contact with a fluid-filled cavity, the amniotic cavity, while the hypoblast contacts the forming yolk sac cavity (Fig. 1). Through the process of gastrulation, two new germ layers are established; a middle (mesodermal) germ layer and an underlying endodermal germ layer that displaces the hypoblast. Thus, cells of the epiblast give rise to the mesodermal cells, as well as to cells of the definitive embryonic endoderm (Poelmann, 1981). These cells migrate inward through a region called the primitive streak, which is composed of the epiblast cells at the caudal midline of the embryo. Following gastrulation, the former epiblast layer is termed ectoderm. The gastrulating cells are laid down in a cranial to caudal sequence, with this process continuing at the caudal end of the embryo through the fourth week of human development. The embryonic disc, thus, becomes trilaminar, with an exception being a region of the cranial midline where only two cell layers are present. The cells subjacent to the median ectoderm at the anteriormost aspect of this bilayer is called the prechordal (prochordal) plate. The cells subjacent to the midline ectoderm which extend

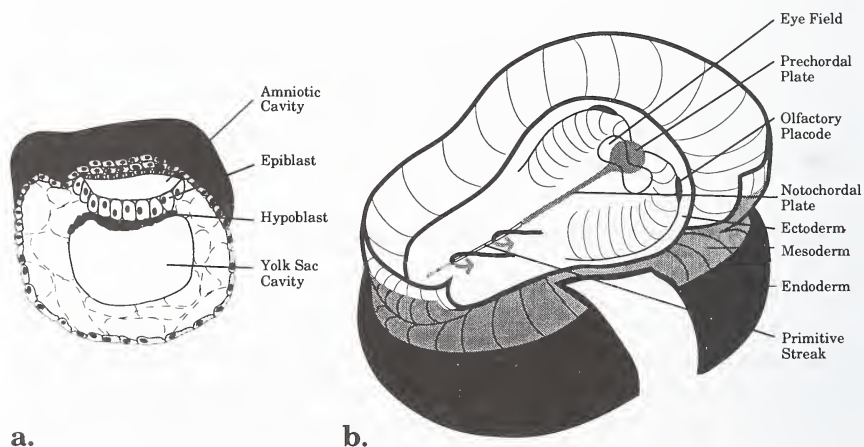


Fig. 1. a) A diagrammatic representation of a cross-sectional view of a human embryo at the beginning of the third week postfertilization. The cells of the inner cell mass have proliferated and become arranged as a bilayered disc. During the third week postfertilization in the human, gastrulation begins, as cells from the epiblast migrate through the primitive streak, as illustrated in b, (Diagrams modified from Tuchmann-Duplessis, 1975.)

from the prechordal plate to the anterior end of the primitive streak is the notochordal plate (Figs. 1 and 2). The cells that constitute the notochordal plate are typically referred to as mesoderm, but they, as well as the cells of the prechordal plate, are continuous laterally with the endoderm. The position of the prechordal plate indicates the region where the primitive oral cavity, the stomodeum, will form. The cardiogenic region is anterior to the prechordal plate in the embryonic disc. Relative differences in growth rate result in a ventrocaudal displacement of the cardiogenic region and the stomodeum (Fig. 3).

The mesoderm, which is located just lateral to the midline (paraxial mesoderm) in the developing cranial region, is initially incompletely segmented as "somitomes" (Fig. 4) (Meir and Tam, 1982). The somitomes, which provide the first evidence of a segmental pattern for the head, are believed to be analogous to the more readily detectable mesodermal segments of the trunk, the somites. Seven somitomes form in a cranial to caudal sequence from the region of the developing prosencephalon to the occipital region, each one being associated with a specific portion of the cranial neural plate. The somitomeric mesoderm gives rise to the muscle cells associated with the visceral arches as well as to the skeletal tissue of a major portion of the calvaria (the upper part of the skull). The mesoderm, which is positioned lateral to the somitomeric mesoderm in the head, differs from its analogous component in the trunk, the lateral plate mesoderm, in that it does not separate into two distinct layers representing a splanchnopleure and somatopleure (Fig. 4).

As gastrulation proceeds, neurulation, the process that results in the formation of the nervous system, begins. The cells subjacent to the ectodermal cells of the neural plate, particularly those in the midline (the prechordal and notochordal plates), exert an inductive influence that is necessary for neurulation. The ectoderm, which forms the neural plate, remains thick (the epiblast cells constitute a columnar epithelial sheet) and become distinguishable from the more laterally lying presumptive surface ectoderm as the latter population thins, becoming squamous (Verwoerd and van Oostrom, 1979; Morriss-Kay, 1981) (compare Figs. 2d. and 4c.). Changes in the shape of the neural plate (Figs. 2-4), as it develops into the regions that are distinguishable as the future forebrain (prosencephalon), midbrain (mesencephalon), and hindbrain (rhombencephalon), and as it folds to form the neural tube, are dependent upon differential rates of mitosis, normal cellular degeneration (physiological cell death) (Poelmann, 1980), and cytoskeletal and extracellular matrix components. In addition, Morriss-Kay and Tuckett (1987) have recently shown, using 2-13 somite mouse embryos as a model system (comparable to the human in the late third to early fourth weeks postfertilization), that rapid development of the forebrain relative to more caudal parts of the developing brain occurs as a result of the cranialward displacement of neuroepithelial

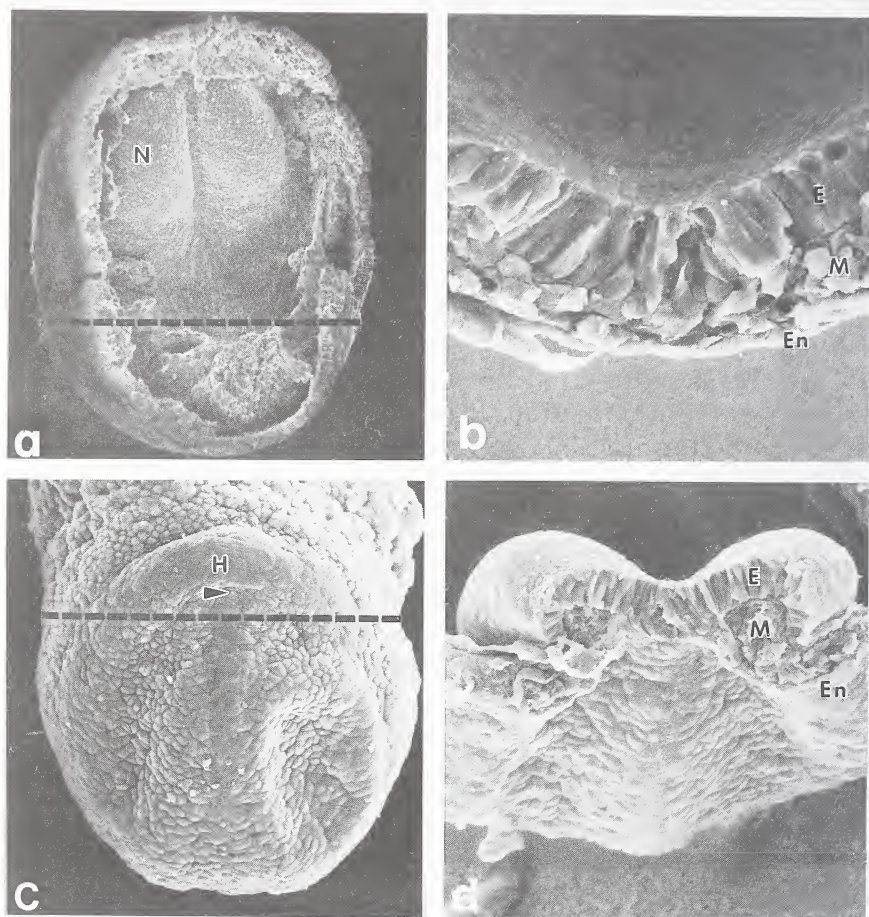


Fig. 2. Scanning electron micrographs of gastrulation stage mouse embryos. A dorsal view (a) illustrates the developing neural plate (N). A cut through the caudal end of the embryo at the position of the dotted line reveals the morphology of the primitive streak as shown in (b). A ventral view of the embryo as shown in (c) illustrates the position of the cardiogenic area (H) anterior to the prechordal plate (arrowhead). A cut through the anterior end of the embryo as indicated by the dotted line reveals the morphology as shown in (d). It is evident that a bilayer of cells occupies the midline. The ectoderm (E) is columnar, the mesoderm (M) forms a relatively loose mesenchyme, and the endoderm (En) is a squamous layer. [a, from Sulik and Johnston, 1982; b, c, d from Sulik and Schoenwolf, 1985 with permissions from the publishers.]

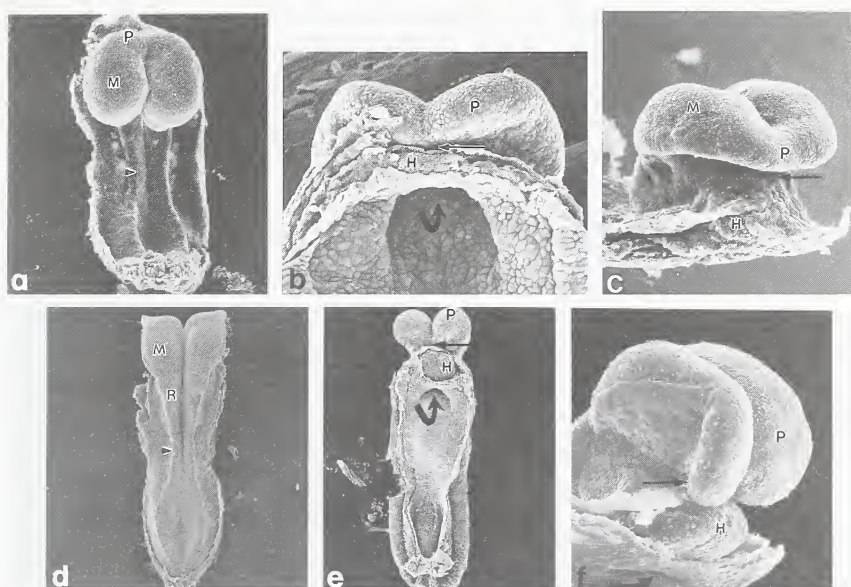


Fig. 3. Scanning electron micrographs of neurulating mouse embryos (a-f). Three distinct regions of the developing brain, the forebrain (prosencephalon; P), midbrain (mesencephalon; M), and hindbrain (rhombencephalon; R) become evident at a time corresponding to the fourth week postfertilization in the human. Dorsal views (a and d) illustrate the developing brain and spinal cord. The neural folds (arrowheads) have not yet begun to fuse. Ventral views (b and e) illustrate the relationships of the forebrain (P), stomodeum (straight arrow), heart (H), and foregut (curved arrow). The forebrain enlarges at a more rapid rate than the other regions of the brain (compare c and f). [a from Sulik and Johnston, 1982; c from Johnston and Sulik, 1984; e and f from Sulik and Schoenwolf, 1985]

cells from levels caudal to the forebrain. Thus, at these early stages, the developing forebrain, which constitutes a very small part of the anterior aspect of the neural plate in 2–3 somite embryos, is, to a large extent, dependent for its rapid growth on the proliferation and displacement of neuroectodermal cells from the initially larger midbrain and upper hindbrain regions.

Segmentation of the cephalic neural plate into the forebrain, midbrain and hindbrain, with further subdivision of the midbrain into two neuromeres and the hindbrain into four neuromeres, is presaged by the somitomeres; each of the somitomeres being located at the level of subsequent formation of the neuromeres. The forebrain develops in relationship to the first somitomere, etc. (Fig. 4). The neuromeres (which undergo subsequent subdivision at hindbrain levels) are evident prior to the time of complete cephalic neural tube closure in the mammal.

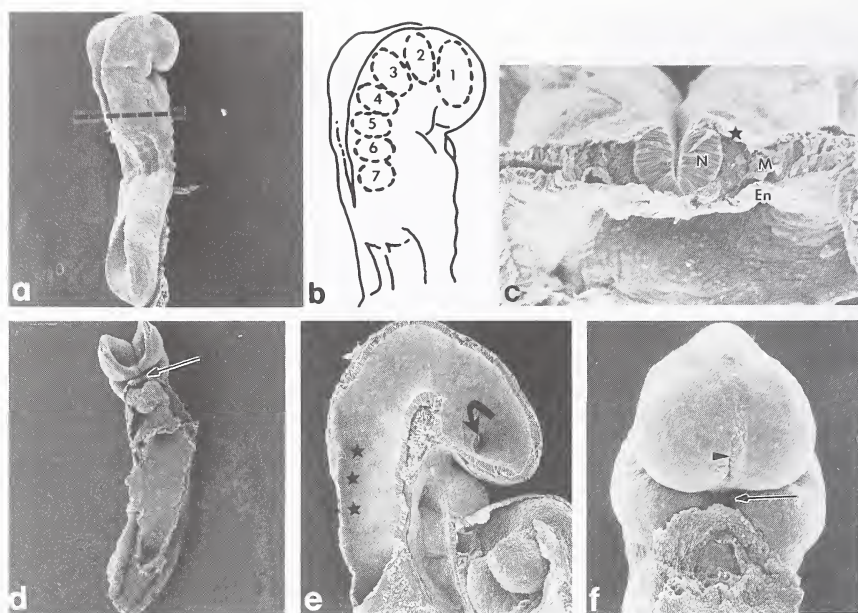


Fig. 4. The relationships between the developing brain (neural ectoderm), surface ectoderm, and the subjacent mesoderm, are illustrated in a–f. In a note that the neural tube has begun to close; the dashed line is representative of the level of the cut for c. Although segmentation of the cranial paraxial mesoderm is no longer evident at the stages illustrated in this plate, the positions of the (former) somitomeres relative to the brain are indicated in b, which is a line drawing of the cranial region in a. The somitomeres presage the development of morphologically distinct neuromeres (stars), as are evident in the hindbrain and illustrated in an embryo that has been cut midsagittally. Star in c, surface ectoderm, N, neural ectoderm, M, mesoderm, En, endoderm, curved arrow, optic stalk, straight arrow, stomodeum, arrowhead, anterior neuropore [d, e, f from Sulik and Schoenwolf, 1985]

Cephalic neural tube closure is completed during the latter part of the fourth week of human gestation (at the time when approximately 20 somite pairs are present). In the human, closure of the neural tube progresses both cranially and caudally, beginning at the level of the fourth somite. Cranial neural tube closure in the mouse is a bit more complex, as progression of cephalic closure does not follow one caudal to cranial sequence. A second point of fusion occurs in the forebrain and closure also proceeds both rostrally and caudally from this site (Geelen and Langman, 1977).

Fate maps of the presumptive forebrain from three to four somite stage avian embryos have been generated (Couly and LeDouarin, 1987). An

intimate relationship has been shown to exist between the cephalic neural folds and the presumptive olfactory placodes (Fig. 1b) and the surface ectoderm of the upper midface. Mapping studies have shown these surface ectodermal components to be initially located on the rim of the anterior neural plate. Additionally, the presumptive optic neuroectoderm is located in the central aspect of the developing forebrain at this stage.

B. Neural Crest

As the neural folds elevate, but prior to their fusion at preotic levels in the mammal, cells located at the junction between the surface ectoderm and neural plate on each side, begin to leave the ectodermal layer, becoming mesenchymal (ie, forming loose connective tissue) (Fig. 5). In the mouse, for the most part, the neural crest cells leave the neural folds in a cranial to caudal sequence, an exception being the slightly later emigration of the forebrain versus midbrain-associated crest cells. The cells from the various levels of the neural folds populate specific regions (although there may be some overlap), with those from the forebrain and upper mesencephalic levels populating the region of the frontonasal prominence; those from the lower mesencephalic and upper hindbrain regions populating the presumptive maxillary and mandibular regions, etc (Fig. 5d) (Nichols, 1981, 1986; Tan and Morriss-Kay, 1985; 1986). The majority of the newly formed ectomesenchyme at cranial levels, as opposed to that in the trunk, is located immediately subjacent to the surface ectoderm. In the trunk, most of the neural crest cells migrate more deeply, through the cranial half of each somite. Evidence indicates that at least some of the "displacement" of cranial neural crest cells in the mammal is due not to active migration, but to "deposition"; ie, as the neural folds elevate, the crest cells are left behind at their original level (Vermeij-Keers and Poelmann, 1980; Nichols, 1986).

Although the neural crest cells derived from all levels of the neural folds play a significant role throughout the body as they differentiate into pigment cells, nerve cells (both sensory and motor), and glial cells; in the craniofacial region, they are of particular importance (Johnston, 1966; LeDouarin, 1982; reviewed by Noden, 1988). As opposed to the trunk, where skeletal and connective tissues are mesodermally derived, in the head, much of the skeletal and connective tissue is neural crest-derived. All of the skeletal and connective tissue components of the face (with the exception of the enamel of the teeth), including dentin, cartilage, bone, and the connective tissue surrounding blood vessels, glands, and muscle, and the dermis, smooth muscle and adipose tissue of the skin are neural crest-derived. Additionally, the meninges of the forebrain, the corneal endothelium and stroma, and most of the sclera and the ciliary muscles of the eye are of neural crest origin. Figure 8a (below)

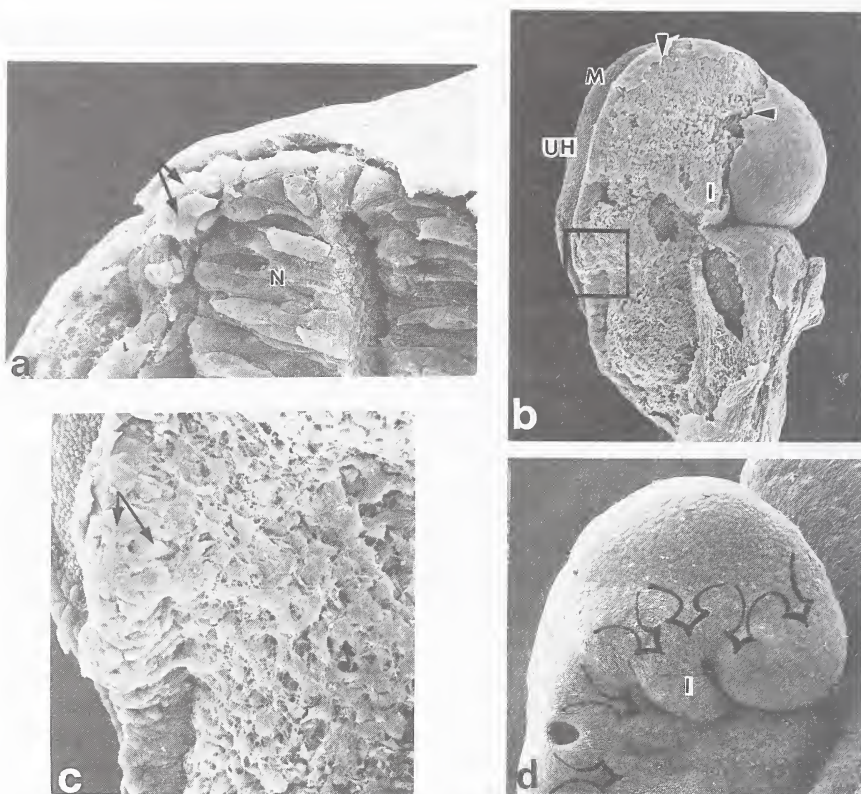


Fig. 5. Emigration of the neural crest cells cranial to the otocyst, as opposed to that in the trunk, begins prior to neural tube closure in mammals, as illustrated in (a–d). A cut made at the level of the trunk (a), shows neural crest cells (arrows) leaving the closed neural tube (N). Removal of the surface ectoderm (arrowheads) in the cranial region at a time preceding neural tube closure shows the subjacent neural crest cell population (b). The box in (b) outlines the area shown at higher magnification in (c) which shows the crest cells (arrows) emigrating from the hindbrain to enter the region of the second visceral arch. Arrows in (d) indicate the general relationship between the brain level of origin and the destination of neural crest populations. I = first visceral arch; M = midbrain; UH = upper hindbrain.

illustrates the territories in the craniofacial region in which the skeletal and connective tissue components are of neural crest origin as opposed to mesodermal origin. Experimental evidence has shown that spatial information involved in proper patterning of the craniofacial skeletal, muscular, vascular, and peripheral neural tissue is contained in the connective tissue precursors (reviewed by Noden, 1988). It is believed that the connective tissue precursors

of neural crest origin acquire their spatial programming while still associated with (or as part of) the central nervous system.

As previously noted, some of the cranial neural crest cells give rise to sensory neurons. In the head, sensory neurons are also derived from placodes (a term referring to thick surface ectoderm): the olfactory, otic, trigeminal and epibranchial placodes (Figs. 6 and 7).

C. Development of the Face and Visceral Arches

At the time of anterior neuropore closure, the tissue surrounding the developing forebrain, the frontonasal prominence, has a smooth, rounded external contour (Figs. 4 and 5). The position of the nasal (olfactory) placodes is evident upon surface examination a short time later (Fig. 6). These two areas of thick ectoderm located on the fronto-lateral aspects of the frontonasal

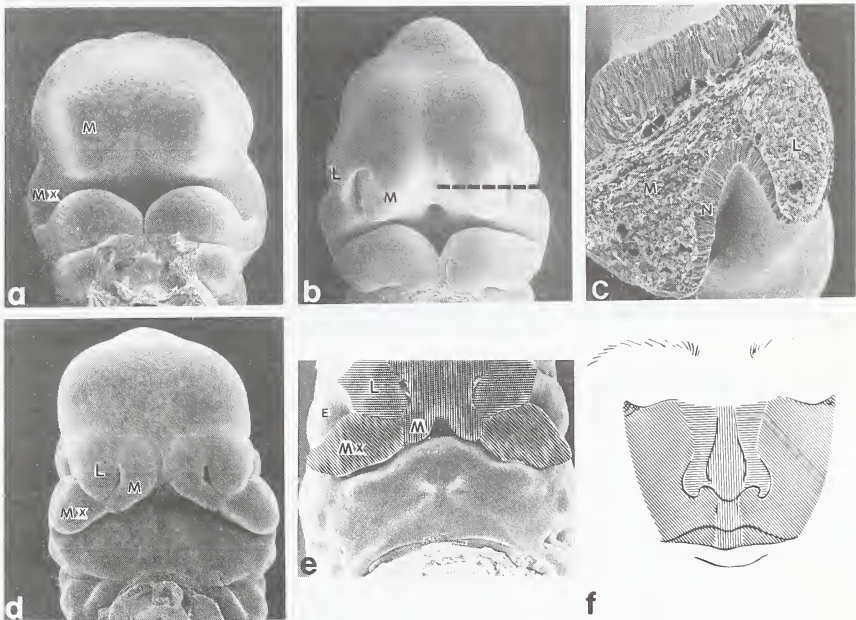


Fig. 6. Development of the portion of the face above the oral cavity centers around formation and fusion of the medial (M) and lateral (L) nasal, and maxillary (Mx) prominences, as illustrated in (a-d). A cut through the nasal pit at the level indicated by the dotted line in (b) illustrates the thickness of the nasal or olfactory placode (N) relative to the surface ectoderm (c). Contributions of the facial prominences to the adult face are shown in (e and f). The specimen in (e) is a human embryo, while the other specimens illustrated in this plate are mice. E = eye [a from Sulik and Johnston, 1983; c and d from Sulik and Schoenwolf, 1985; b, e, f from Sulik and Johnston, 1982]

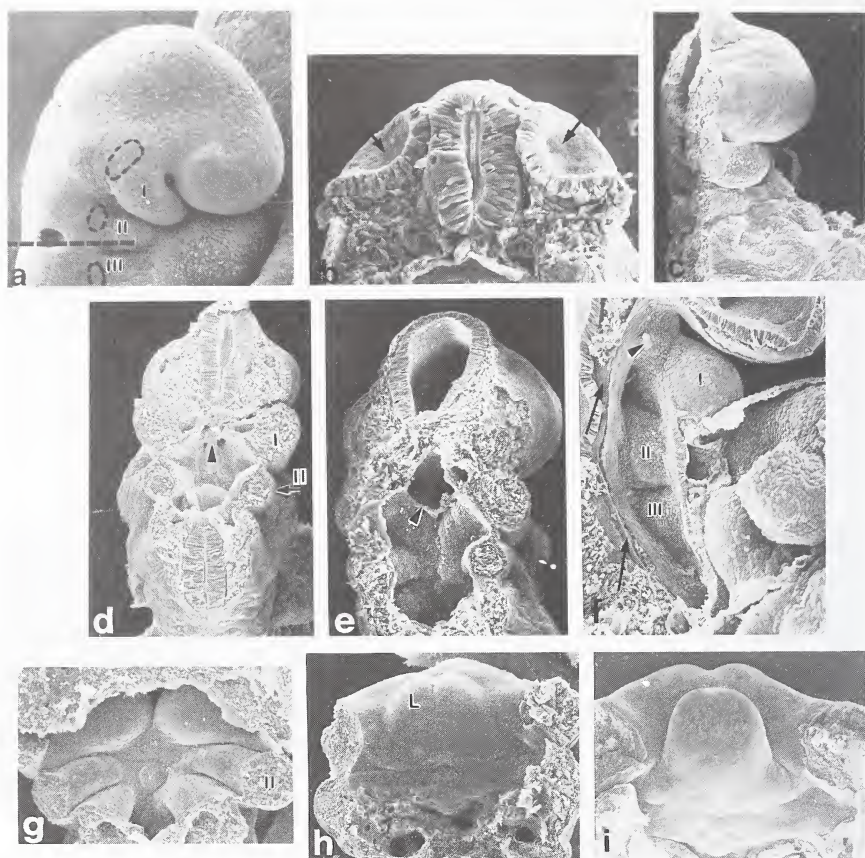


Fig. 7. The visceral arches, which develop in a cranial to caudal sequence, are separated externally by grooves and internally by pouches, as illustrated in (a, c-e-g). The invaginating otic placodes (arrows in b, which is from a specimen cut at the level of the dashed line in a) are in close association with the neural tube and will form the internal ears, as well as the sensory neurons associated with them. Other ectodermal placodes are located as outlined by the dashed lines in a. The trigeminal placode (located at the proximal aspect of the first arch) and epibranchial placodes (shown at the proximal aspects of the second and third arches) contribute cells to the cranial nerve ganglia. Frontal (c and d are the same embryo, and e is a slightly older specimen) as well as midsagittal f fractures through embryos at this time allow visualization of the breakdown of the buccopharyngeal membrane (arrowheads), which allows continuity between the stomodeum and pharynx c-e. Additionally, the mesenchymal cores of the arches and the position of the pouches can be seen. Note the position of the notochord (arrows in f) which extends only as far forward as the remnant of the buccopharyngeal membrane. The tongue develops from the ventral aspect of the visceral arches, with the first arch contributing the lateral lingual swellings (L; the anterior $\frac{2}{3}$ of the tongue), and the second through fourth arches contributing to the posterior third (g-i). I = first visceral arch; II = second visceral arch; III = third visceral arch [c and d from Johnston and Sulik, 1980; f from Sulik and Schoenwolf, 1985; g and i from Johnston and Sulik, 1984]

prominence are apparent as nasal pits, surrounded by tissue elevations termed the nasal prominences (processes). A reciprocal relationship exists between the nasal placodes and the olfactory fields of the forebrain; ie, they are mutually dependent for normal growth and development (reviewed by Bossy, 1980).

The nasal prominences develop into the nose, as their name implies (Fig. 6). The lower portions of the medial nasal prominences also contribute to the upper lip, and form the portion of the alveolar ridge which contains the upper four incisors as well as the associated part of the hard palate that is termed the primary palate. On each side of the developing face, fusion of the medial nasal prominence with the lateral nasal prominence and the maxillary prominence of the first visceral arch is required for normal formation of the upper lip.

The visceral (pharyngeal, branchial) arches form in a cranial to caudal sequence on the ventrolateral aspect of the developing face and neck (Figs. 7 and 8). These bars of tissue (containing cells of both mesodermal and neural crest origin) are delineated from one another externally by grooves, and internally by pouches. The visceral arches initially serve as conduits for blood vessels, the aortic arch arteries. Each of the arches is associated with specific cranial nerves, and has specific muscular and skeletal derivatives (Table 1). The muscular components are mesodermally derived, while the connective tissue components are derived from neural crest cells.

The first visceral arch is evident in embryos having 15 somite pairs. This arch initially appears as a single prominence of tissue (Fig. 7). By the time the embryo has 30 somites, two distinct areas, the maxillary and mandibular prominences, are apparent. These are generally (although, perhaps, inappropriately relative to the maxillary prominences) both considered as part of the first arch (Fig. 8). Neural crest cells derived from mesencephalic and upper hindbrain levels, initially form most, if not all, of the mesenchyme of the maxillary prominences. These prominences contribute the majority of the tissue of the upper jaw. As previously noted, they fuse with the medial nasal prominences in the course of normal development of the upper lip. The maxillary prominences also form the majority of the hard palate; the portion termed the secondary palate. The secondary palatal shelves can be observed, in the mouse, growing down on each side of the tongue at developmental stages corresponding to that of humans in the seventh and eighth weeks postfertilization (Fig. 8e). Prior to their union in the midline, and prior to their union with the primary palate and the nasal septum, which occurs early in the ninth week in the human, they come to lie above the tongue (Fig. 8f).

The mesenchymal population of the mandibular prominences initially consists of mesodermal cells. Neural crest cells from the level of the lower midbrain and upper hindbrain join the mesodermal cells to populate these

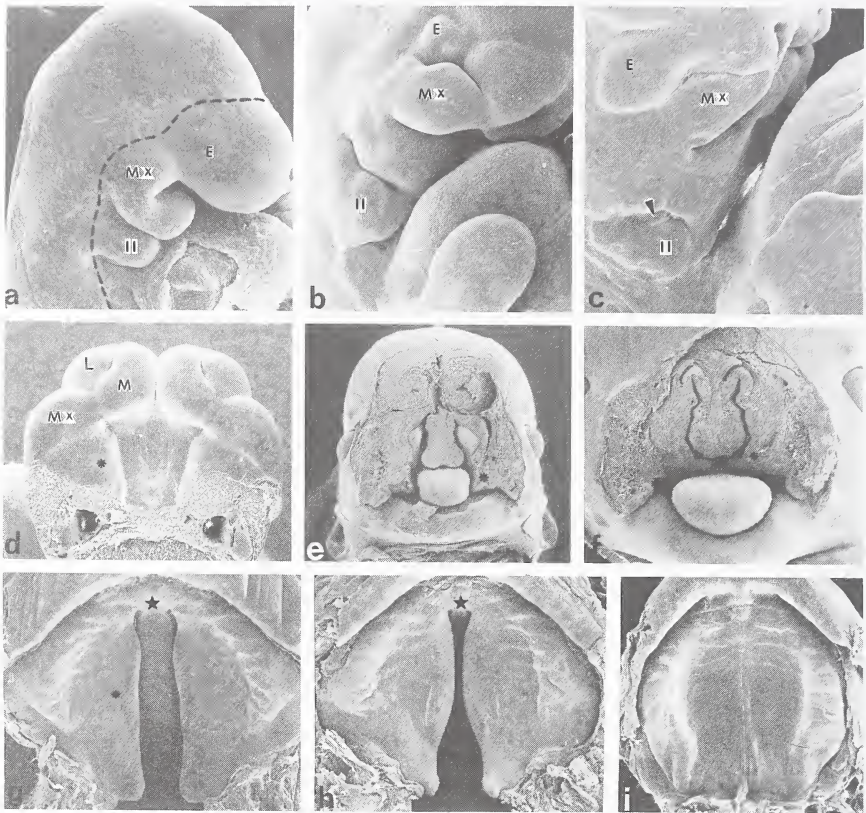


Fig. 8. Development of the external lateral surface of the head proceeds with the external ear forming from the first and second visceral arches (a-c; arrowhead in c = external auditory meatus, which is surrounded by the auricular hillocks). The dashed line in (a) indicates the separation of the territories from which skeletal and connective tissue components are neural crest derived (ventral portion) versus mesodermally derived (dorsal portion). A cut through the corners of the mouth (d) or frontally, through the nose (e, f), allows visualization of the developing palate. The primary palate (stars in g and h) is composed of tissue from the medial nasal prominences (M), while the secondary palate (asterisk) is of maxillary prominence (Mx) origin. The secondary palatal shelves reorient to become positioned above the tongue, allowing fusion in the midline (e-i). Specimens in (c, g-i) are human (courtesy of Dr. L. Russell). [b, c, e, f from Sulik and Schoenwolf, 1985; d from Johnston and Sulik, 1980]

TABLE 1. The Visceral Arches and Pouches

Arch	Nerve	Muscles	Skeleton and Ligaments	Pouch	Derivatives
1. Mandibular	V. Trigeminal	Muscles of mastication, mylohyoid, anterior belly of digastric, tensor veli palatini, tensor tympani	Meckel's cartilage, sphenomandibular ligament, malleus, incus	First Second Third	Eustachian tube Palatine tonsils Thymus gland and inferior parathyroid glands
2. Hyoid	VII. Facial	Muscles of facial expression, posterior belly of digastric, stylohyoid, stapedius	Styloid process, stapes, stylohyoid ligament, lesser horn and upper portion of the body of the hyoid bone	Fourth Fifth	Superior parathyroid glands Ultimobranchial bodies
3.	IX. Glossopharyngeal	Stylopharyngeus	Greater horn and lower portion of the body of the hyoid bone Laryngeal cartilages		
4-6.	X. Vagus	Levator veli palatini, laryngeal, pharyngeal constrictors			

prominences. The lower jaw and a large portion of the tongue are major derivatives of the mandibular prominences.

Tissues from both the first (mandibular) and second (hyoid) arches contribute to the external ears, with three auricular hillocks (on each side) forming from each (Fig. 8c). The bones of the middle ear also originate from tissues of these two visceral arches.

Scanning electron microscopic views of embryos that have been cut through the first and second visceral arches in the coronal plane reveal the relationship between the visceral arches, pouches and grooves (Fig. 7). In addition, the breakdown of the buccopharyngeal membrane (tissue which is believed to be analogous to the anteriormost aspect of the prechordal plate), which results in continuity between the primitive oral cavity (stomodeum) and the pharynx can be observed. The epithelium on the stomodeal side of this membrane is ectodermally derived, whereas that on the pharyngeal side is endodermal. The definitive position of this ectodermal-endodermal boundary is just in front of the palatine tonsils.

The tongue is derived from tissue originating from the distal aspect of the first four visceral arches. However, the tongue is somewhat unusual in that its voluntary muscular component, which is innervated by the 12th cranial nerve, is derived from mesodermal tissue from occipital (postotic) somites.

D. Ocular Development

The ectoderm that is destined to form the neural and pigmented retina, as well as a significant portion of the iris and ciliary body of the eye, originates at presomite stages in the central aspect of the anterior neural plate. Using scanning electron microscopy, the position of the optic neural ectoderm is evidenced in embryos having six to nine somite pairs, as two depressions (evaginations) termed optic sulci, each of which is centrally placed in the developing prosencephalic hemispheres (Fig. 9). As the anterior neural folds close, the optic evaginations, now termed optic vesicles (connected to the forebrain by the optic stalks), closely approximate the surface ectoderm. The surface ectoderm in the region of this approximation is induced to become columnar, forming the lens placode. Invagination of the optic vesicles to form the bilayered (neural and pigmented) optic cup is accompanied by invagination of the lens placode to form the lens vesicle. Following separation of the lens vesicle from the surface ectoderm, the cornea develops. While the ectoderm forms the epithelium of this structure, all of the subjacent layers are derived from cells of neural crest origin. Neural crest-derived cells also enter the vitreous space, surrounding the vascular endothelia, which are of mesodermal origin. Additionally, neural crest cells form the musculature of the ciliary apparatus, whereas the muscles of the iris are derived directly from the neural ectoderm at the margin of the optic cup.

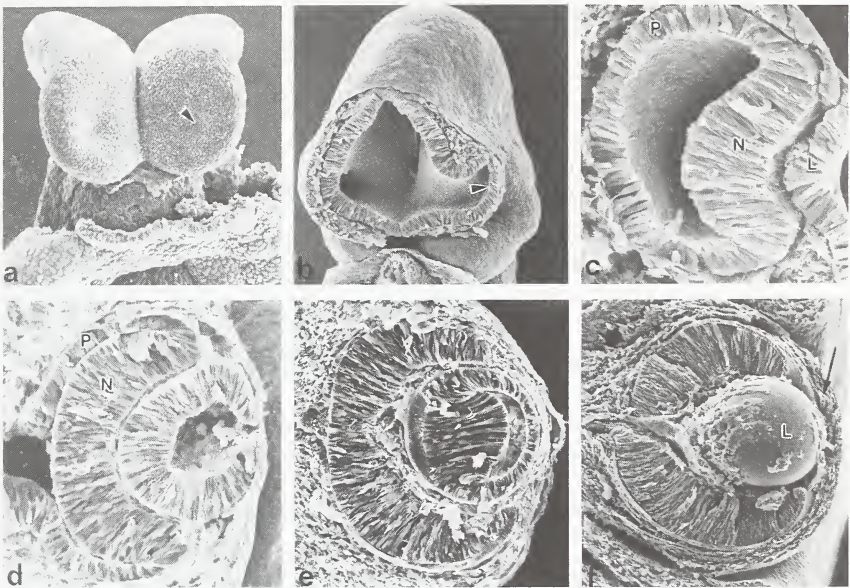


Fig. 9. Ocular development is well illustrated using scanning electron microscopy (a-f). This includes evagination of the optic vesicle (arrowheads in a and b), development and invagination of the lens (L) placode, which is concurrent with optic cup formation, and formation of the cornea (arrow in f). N = neural retina; P = pigmented retina [b from Johnston and Sulik, 1984; c from Cook and Sulik, 1986; d, e, f from Sulik and Schoenwolf, 1985]

III. ABNORMAL CRANIOFACIAL EMBRYOGENESIS

Utilizing acute exposures to environmental agents, malformations can be induced in animal models at known developmental stages. For example, acute maternal treatment of C57Bl/6J mice with alcohol at the initial stages of gastrulation in the embryos (gestational day 7; corresponding to the third week postfertilization in the human) results in a midline deficiency in the frontonasal prominence and the forebrain. Severely affected specimens have holoprosencephaly (a single cerebral hemisphere) and mildly affected specimens have craniofacial features that appear to correspond to those in children having fetal alcohol syndrome (FAS) (Sulik and Johnston, 1983). Comparable treatment 1½ days later in the mouse results in a different spectrum of craniofacial and brain malformations. These have been compared to the facial features seen in the DiGeorge sequence or velocardiofacial syndrome (Sulik et al, 1986). DiGeorge sequence is reported in offspring of alcoholic women as well as those inadvertently exposed to retinoic acid. At the earlier treatment time, the formation of the anterior neural plate and the process of gastrulation

are affected. This appears to result, at least in part, from excessive amounts of cell death in the epiblast (Sulik et al, 1988). Cells that appear to be primarily affected at the later treatment time include neural crest and/or placodal cells.

Retinoic acid is a potent human teratogen. Marketed under the trade name of Accutane, inadvertent exposure to this drug has resulted in a malformation pattern that is termed "retinoic acid embryopathy (RAE)" (Lammer et al, 1985). First and second visceral arch-derived tissues show major effects, but involvement is not limited to facial structures. Animal models of RAE indicate that the visceral arch abnormalities may result from excessive cell death in neural crest cells prior to their migration and/or interference with migrating crest cells (Webster et al, 1986). The critical exposure period in this animal model corresponds to approximately 20–23 days postfertilization in the human.

Administered at slightly later stages in gestation in animal models, retinoic acid can cause a malformation pattern which is similar to that in individuals with mandibulofacial dysostosis (Treacher Collins syndrome). Individuals with this syndrome have deficiencies involving the zygomatic region, mandibular ramus and condyle, external ear and secondary palate. Recent studies have provided evidence that excessive cell death at the proximal aspect of the maxillary and mandibular prominences of the first visceral arch (cells associated with the trigeminal placode) is involved in the pathogenesis of this syndrome (Sulik et al, 1987). Critical periods in human gestation appear to be from approximately 23–26 days postfertilization.

In addition to exposure to environmental agents, animal models having genetic mutations are providing important clues relative to mechanisms of malformation. An example is a mouse mutation that was created using transgenic technology. Insertion of foreign DNA into mouse embryos resulted in a mutation, which in the homozygous state, yields abnormal individuals having features of frontonasal dysplasia and limb abnormalities (McNeish et al, 1990). The technology exists to localize the mutation and to determine how the genome is altered in the abnormal individuals. These studies are under way.

IV. CONCLUSIONS

Within the past few years, our understanding of the pathogenesis of a number of craniofacial malformations has greatly improved. In part, this has resulted from the development of suitable animal models, the use of modern techniques for scientific investigation, and our increasing base of knowledge relative to normal embryology and cell biology. This is an exciting time for teratologists as the pieces begin to fall into place; we can appreciate the

critical periods, and the basis for involvement of specific cell populations in the pathogenesis of a variety of malformations.

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Fetal Diagnosis and Therapy: An Update*

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This presentation includes a discussion of methods of fetal sampling and treatment, and their current status. The following procedures comprise the "state of the art" in prenatal detection and treatment of genetic and chromosomal conditions. A look to the future is also included.

Chorionic villus sampling (CVS): The information available today is from two collaborative studies—the Canadian study and the American study. The Canadian study and the first part of the American study compared transcervical CVS (TC) and amniocentesis. The American study has been extended to include a randomized comparison between TC CVS and transabdominal (TA) CVS. The results of the latter will be published in late 1990. Both studies revealed that there is no difficulty in obtaining a diagnosis on CVS. However, in 1% of cases, a second test, usually amniocentesis and occasionally percutaneous umbilical blood sampling (PUBS), will be required to arrive at an accurate result.

With regard to the risk of miscarriage, both studies findings were essentially the same: a 0.8% higher loss rate in TC CVS than in amniocentesis (USA) and a 0.6% higher loss rate in TC CVS than in amniocentesis (Canada). The CVS losses occurred earlier in pregnancy in the US study than in the Canadian study. The losses after 20 weeks in the Canadian study are not explained. In both studies, the increased loss rate is not statistically significant. However, we are using the information that the loss rate is higher in CVS than amniocentesis in our counseling; and saying the difference is not statistically significant. The implementation of TA CVS will change things: some patients who were difficult to sample transcervically and who may have had complications now would be done transabdominally. Today, the safest, easiest procedure is chosen for each patient. "Ease" constitutes avoiding the factors associated with the increased risk of pregnancy loss. Three of these factors reflect a mechanically difficult procedure: a fundal placenta, multiple passages of the catheter, and obtaining a small amount of villi. The fourth factor is a history of early bleeding, often a sign of impending miscarriage. This factor may not be procedure related, but a natural consequence unrelated to CVS. Many other factors were examined; none had any statistically significant effect.

*This is a transcription of Dr. Golbus's oral presentation.

One of the biggest problems with CVS is the 1% of patients with mosaic results on either direct or tissue culture analysis. Superficial trophoblast cells are studied by direct method, while the core of the villus is examined with the tissue culture method. Mosaicism has been observed in both cultures; the culture mosaicism is confirmed more frequently than the direct mosaicism. It appears that the cultured villi more accurately represent the fetal karyotype. The study revealed that less than 25% of mosaics were confirmed; the mosaicism is confined to placenta in most cases. These data suggest that these are early mitotic errors and that a selectivity is operating in terms of which cells become part of the embryo. These mosaic results present unique counseling issues. Amniocentesis, often early amniocentesis, would be offered if the trisomy were one that is not seen clinically in liveborns. If the abnormal cell line is clinically significant, such as trisomy 21, we also offer percutaneous umbilical blood sampling (PUBS) in order to obtain true fetal tissue.

Discordance data reported in the American Collaborative study revealed that, in the majority of cases, the culture result is confirmed in fetal tissue. Abnormal direct results with normal tissue culture findings are usually false-positive for the direct analysis. While some centers do both direct and tissue culture, it is suspected that new centers most likely will perform tissue culture only. An interactive computerized system decreases the time necessary to report results.

Another question regarding CVS safety is the comparison of miscarriage rates between transcervical (TC) and transabdominal (TA) CVS. When reading these studies, it is important to notice the difference in definition of "pregnancy loss." There has been one randomized study completed—a Danish study—which reported a higher loss rate from TC than from TA. The losses included spontaneous abortions up to full term and those with chromosomal abnormalities. In Milan, Italy, the TC rate was also higher than that after TA. In the U.S., TA had a slightly higher loss rate than TC in the Chicago, Philadelphia and San Francisco series. The continuation of the NIH study analyzed nearly 4,000 patients who were randomly assigned to have TC or TA CVS. Enrollment ended in September, 1989; results should be published in late 1990. It appears that there are data to support both sides in different studies; it all averages out in the end. I think there will not be a difference in risk once the randomized trial is complete. It appears that the procedural loss rate is approaching the biologic, background loss rate.

Some centers are performing "late CVS"—that is, after 12 weeks. TC CVS after 12 weeks is difficult to perform; most centers will stop by the end of the first trimester. TA CVS is performed in some centers, especially when an abnormal sonogram identifies the need for rapid chromosomal analysis. If PUBS is not readily available, TA CVS has become an alternative. The loss rates are difficult to assess since fetuses with anomalies identified on ultra-

sound are more likely to be chromosomally abnormal and to be miscarried. Many centers will perform TA CVS after 12 weeks because a patient is farther along in her pregnancy. The total loss rates in the early CVS maternal age group and the late CVS group do not appear to be different when abnormalities, spontaneous losses and elective terminations are considered. Late CVS, done after sonographic abnormalities are detected, offers the patient an opportunity for earlier termination, if this is the patient's decision.

Approximately 1% of patients who have normal CVS results terminate their pregnancies for personal/social reasons. A major issue of concern is that of terminations performed for sex selection. There have been some instances of sex selection where the patient did not indicate that this was the purpose of testing. Fortunately, the incidence in all participating centers has been low.

Prenatal diagnosis of sex chromosome abnormalities has always posed dilemmas for families considering continuation or termination of pregnancy. The NIH study revealed that 71% of the amniocentesis patients terminated, while nearly 97% of CVS patients made the same decision. When an autosomal abnormality was diagnosed, about 99% of CVS patients and 90% of amniocentesis patients terminated their pregnancies. These data support the assumption we made at the start of the program regarding the advantage of first trimester prenatal diagnosis.

Early amniocentesis: performed between 12 and 15 weeks of gestation, is being performed in many centers. There are insufficient data available at this time to assess the risks of this test. The loss rate is one concern, but I believe we must examine the possibility of increased risk for joint problems such as hip dislocation and respiratory distress syndrome. These were reported in the British "standard" amniocentesis study, but not substantiated in the American or Canadian studies. It behooves us to carry out careful examinations on a large number of infants before claiming safety for early amniocentesis. Currently, the American College of Obstetrics and Gynecology, with support from the March of Dimes Birth Defects Foundation, is collecting data from centers who are voluntarily submitting statistical information on their experience with early amniocentesis. Drawbacks to this approach include the fact that this study is not randomized and that there is no control over what data are reported by contributors. It is certainly our responsibility to collect data on early amniocentesis for the public.

PUBS, or fetal blood sampling: this is another method of sampling fetal tissue for prenatal diagnosis. There have been no recent changes in this technology. The reason for doing PUBS in over 50% of cases is the detection of an abnormality by ultrasound resulting in the need for a rapid karyotype. PUBS is also used to monitor fetal hematocrits in Rh-immunized patients before and after transfusions.

Fetal liver biopsy: this has been performed in a few cases worldwide. Nine procedures were done at our center; Dr. Rodeck in London has also performed biopsies. This technique is utilized in patients who are uninformative for DNA diagnosis of ornithine transcarbamylase deficiency, CPS deficiency or glucose 6-phosphatase deficiency.

The fetal sampling technique of the future is noninvasive involving isolating fetal cells from a maternal blood sample and performing genetic or chromosomal analysis on these cells. Several technologies are under investigation. First, a fluorescence-activated cell sorter (FACS) is utilized. The FACS must sort out about one fetal cell for every million maternal cells. Maternal blood is drawn and treated to lyse red blood cells. We want a suspension of nucleated cells in a system whereby cells come out individually in tiny droplets. Then, we must distinguish fetal from maternal cells. Several immunologic techniques utilizing fluorescent antibodies are being tested for sorting maternal from fetal cells. Once fetal cells are isolated, DNA, biochemical or chromosomal analysis can be performed. Issues such as signal:noise ratio (maternal contamination), sensitivity, and specificity must be resolved. These techniques must "capture a rare event." We hope that the results of this type of research will be available and applicable in the near future.

Selective termination of fetuses in multiple gestations has become available in situations where one of a multiple gestation is diagnosed with a chromosome or genetic abnormality. It is also utilized to reduce the number of gestational sacs in the case of multiple gestations often resulting from fertility treatment or in vitro fertilization (IVF).

Historically, this technique was developed for use in the second trimester following amniocentesis. Initially, when one of twins was found to have an abnormality, either both twins would have to be terminated, or the pregnancy had to continue with both twins. Selective termination can be used only with dichorionic twins because monochorionic twins share circulation. The use of methods such as exsanguination and introduction of an air embolism was not successful or safe. Today, infusion of potassium chloride into the heart results in rapid cessation of heart activity. This is a rapid, simple procedure to perform. However, the surviving twins tend to deliver earlier than normal singletons. A hysterotomy, where the abnormal twin is removed after surgically entering the uterus, is performed for monochorionic twins. Three out of four of these procedures were successful, resulting in healthy, premature babies. Monochorionic twins discordant for a genetic abnormality are very rare. Newer, simpler techniques are being explored.

Selective termination or fetal reduction in the first trimester has become more frequent due to the increase in multiple gestations resulting from the use of fertility drugs and IVF. The potassium chloride method is used in the first trimester under ultrasound guidance. It is preferred to reduce the number of

gestations to twins to increase the chance of going full term. Because many of the mothers are over 35, if one twin were chromosomally abnormal, there would still be one twin left. Studies to examine risks to infants and mothers of preterm delivery and other complications are ongoing. In this country, reduction of triplets is considered appropriate, while in Europe, it is less common.

Research and consideration of clinical applications of fetal surgery are continuing. Much of this work is being performed at University of California-San Francisco Medical Center (UCSF). Surgical trials are performed on monkeys.

Surgery for three types of defects has been attempted. For example, oligohydramnios due to urinary tract obstruction is treated by marsupialization of the bladder. Originally, catheters had been placed in such patients; survival in cases of bilateral obstruction increased to nearly 50%. The kidney must be evaluated to determine if any function exists before performing surgery. If a kidney is nonfunctional, a catheter or surgery will not help.

Ventricular shunts for ventriculomegaly (hydrocephalus) have been tried. These were not successful; there is a moratorium on these procedures.

Repair of diaphragmatic hernia in utero has been attempted as well. The UCSF group just reported their first survivors of this surgery after seven or eight attempts. Success was influenced by how much fetal liver was present in the chest cavity. More diagnostic work prior to surgery is needed.

The future direction of fetal treatment is not surgery, but fetal therapy. We need to be able to treat or cure the thousands of babies born each year with hemoglobinopathies or immunodeficiencies. In utero stem cell transplantation may result in fewer problems with rejection than does postnatal transplantation. The fetus is a good recipient because it is more immunotolerant since it "doesn't know self from non-self." Research with mouse and monkey models is ongoing. Attempts to transplant human fetuses at UCSF have been performed for fetuses affected with alpha-thalassemia and severe combined immunodeficiency. Determination of the best time in gestation to perform transplants and the development of innovative techniques will make this type of treatment possible in the next few years.

Reproductive Genetics In The 21st Century: Fact and Fantasy

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The year is 1999.

Mrs. Smith is going for a stroll with her baby carriage and meets Mrs. Jones who peers at the twins.

Says Mrs. Smith: "My oldest was an all-natural delivery . . . then Freddy was cesarean . . . Jenny was in vitro . . . and the twins came freeze-dried in their own resealable zip-lock storage bags."

Welcome to the 21st Century!

Now how did we come to this stage of events, you ask? I would like to present to you a detailed chronology of developments in reproductive genetics that occurred in the decade preceding 1999. At the end of 1989, reproductive genetic services provided only postimplantation genetic diagnosis. The approaches were midtrimester amniocentesis, introduced in the late 1960s, chorionic villus sampling introduced in the early 1980s, with percutaneous blood sampling gaining increasing use in the middle 1980s.

At the end of 1989, there was virtually no prenatal treatment available for chromosomal aberrations and most inborn errors of metabolism. If a genetic abnormality were detected, there were only two options available to the patient and physician: the continuation of an affected pregnancy or elective termination. For families at high risk for a genetically abnormal conception, there was only the prospect of repeated pregnancy termination associated with psychologic stress, prevention of pregnancy or acceptance of the high risk for delivery of a child with the genetic disease.

What of Future Developments in Reproductive Genetics?

I anticipate that in the early part of 1990 the first successful preimplantation genetic diagnosis of an X-linked disorder, eg, Duchenne muscular dystrophy, will be reported by an English group, headed by Alan Handyside [1]. Their technique will involve embryonic biopsy of a single blastomere at the 4-cell or 8-cell stage followed by analysis of Y-sequences by the polymerase chain reaction (PCR) to determine the sex of the developing embryo. A continuing concern with this approach will be the possibility of cell differenti-

ation occurring at these early stages and thereby potentially affecting the normal course of development.

One year later, genetic diagnosis prior to implantation will be accomplished by removal of the first polar body from the maturing oocyte and conducting genetic analysis of the DNA within the polar body by means of PCR. The first polar body is formed during oogenesis when the primary oocyte undergoes meiosis I, specifically the reduction phase of meiosis, sometimes termed "reduction-division." It is at the reduction stage that the first polar body is formed and it, like the oocyte, contains one of each of the two homologous chromosomes, ie, half of the total cellular DNA.

In the case where a person has been identified as heterozygous at a gene locus specifically associated with a defined genetic disorder, the following must hold true: if DNA analysis demonstrated that the polar body contains the mutant gene "a," then the corresponding genotype of the oocyte must be "A." If, on the other hand, DNA analysis demonstrated that the polar body contained the standard gene, "A," then the oocyte must contain the mutant gene "a" capable of contributing to the formation of an affected conception. The genotype of the first polar body and hence, the oocyte, would be determined by amplification of its DNA by PCR. Genetic analysis of the first polar body by PCR could be applied to such genetic disorders as cystic fibrosis, alpha-1-antitrypsin, sickle cell anemia, and thalassemia.

A major disadvantage to this approach is that crossing-over can occur between the gene and the centromere. Both the polar body and oocyte will still be heterozygous and therefore, additional studies, eg, biopsy of single blastomere, would have to be conducted on fertilized oocytes carrying the mutant gene form.

The technical aspects of polar body aspiration are simple. Using micromanipulation techniques, a glass pipette is introduced through the zona pellucida, placed in close proximity to the polar body, and then negative suction is gently applied until the polar body is aspirated into the neck of the pipette.

In 1992, preimplantation genetic diagnosis will be accomplished by combining the technique of uterine lavage to obtain embryos at the blastula stage with trophoctoderm biopsy [2]. The trophoctoderm tissue is multicellular and represents the immature chorion. The technique of trophoctoderm biopsy had been first described in 1987 and involved the following steps: 1) incision of the zona pellucida with a glass needle; 2) herniation of a portion of the trophoctoderm through the incision; and 3) excision of the herniated tissue, which could be placed either in tissue culture for expansion of cell volume, thereby permitting chromosomal and biochemical analyses, as well as DNA analyses, or, analyzed directly for DNA mutations by PCR.

Over the next several years, a debate continued over the advantages versus the disadvantages of preimplantation diagnosis. On the positive side, preim-

plantation diagnosis involved the transfer of only unaffected embryos, which circumvented the need for abortion in high-risk families and reduced the psychologic stress accompanying any pregnancy, particularly high-risk pregnancies. On the negative side, preimplantation diagnosis will be expensive, labor intensive and will have a low rate of completed pregnancies. The possibility of using natural cycles, rather than chemically induced oocyte maturation, may offer a cost-effective approach, making preimplantation diagnosis a useful and practical approach to the prevention of genetic diseases. However, since the rate of completed pregnancies with preimplantation diagnostic techniques will not exceed 50%, first trimester chorionic villus sampling will still be the standard approach for high-risk pregnancies until the end of the 20th century.

Amniocentesis and chorionic villus sampling will also continue to require significant procedural expertise, specialized personnel, and expensive equipment. Consequently, both amniocentesis and CVS will be applied to a limited number of at-risk couples. These methods are therefore not suitable in their present form for widespread screening of pregnancies. The desirability of such screening is obvious, as most genetically defective offspring occur in couples considered to be at low risk. An ideal method for screening pregnancies for genetic abnormalities would be one that is noninvasive, rapid, relatively inexpensive, potentially automatable and easy to perform soon after conception. As with any screening method, its specificity might not be as critical as its sensitivity. Abnormalities detected by such a method might lead to more specific confirmatory tests, such as CVS, amniocentesis, and PUBS, and the predictive value of a negative result would be maximized at the expense of the predictive value of a positive result. This was the hope for exploring the possibility of obtaining and analyzing fetal cells present in the maternal circulation for genetic abnormalities.

Publications claiming the presence of fetal cells in maternal circulation as early as 10–14 days after implantation suggest the exciting possibility of performing prenatal genetic diagnoses starting with the simple removal of a sample of the mother's peripheral blood. Three types of fetal cells have reportedly been found in the peripheral blood of pregnant women: 1) syncytiotrophoblast and cytotrophoblast cells, presumably derived from the breaking off of villi from the chorion and their displacement into the maternal circulation; 2) fetal red blood cells; and, 3) fetal mononuclear cells, possibly of lymphocytic origin.

The early evidence consisted of demonstrating structures with the morphology of syncytiotrophoblast in the uterine veins of the gravid uterus. Douglas et al [3] reported such observations 30 years ago, in 1959. With advances in the characterization of the immunology of trophoblast, reagents became available which labelled these cells with some degree of specificity. First, polyclonal

antisera (reviewed by Faulk and Hsi [4]) and then monoclonal antibodies (Lohmeyer et al [5]) became available which recognize antigenic determinants relatively unique to trophoblast plasma membranes. The use of some of these reagents toward isolation and purification of fetal trophoblast from maternal circulation has been the subject of several publications in the past five years [6, 7]. The authors claimed to have isolated trophoblast cells, based on morphology and immune labeling with the reagent used to isolate the cells. However, none have been successful in culturing these isolated cells and none have been successful in any form of genetic analysis, enzymatic, chromosomal, or recombinant DNA. Also, none have attempted multiparameter analysis of these cells with antibodies to multiple antigens known to be expressed simultaneously by trophoblast cells. Such immunologic, genetic and biochemical studies are obviously required before the nature of these purported fetal cells can be equivocally established.

Similarly, antibodies to HLA antigens have been used to isolate and purify cells of fetal origin from maternal blood. This is the original work of Herzenberg and his colleagues [8], first reported in 1979. They identified cells that appeared to express the fluorescent pattern of the Y chromosome in the circulation of pregnant women who subsequently delivered male liveborn. Although the authors admit that they did not know the true nature of these fetal cells, they suspected that they belonged to the lymphoid lineage.

Fetal cells are presumably "rare events" in maternal blood. Golbus and his colleagues (personal communication) estimate that there may be one fetal cell per one million maternal cells. It now becomes apparent that the techniques used in any approach to isolate, purify and study these cells must have the following characteristics: 1) the isolation procedure must be rapid; 2) the isolation procedure must be highly efficient; and, 3) the isolation procedure must be highly specific.

One of the most promising methodologies being investigated is the combination of a specific antifetal antibody conjugated with a fluorochrome followed by flow cytometry and fluorescence activated cell sorting (FACS). The report by the late Sam Latt's group [9] using this technique suggests that with additional refinements, it will be possible to isolate nucleated fetal red blood cells and analyze fetal DNA by means of the polymerase chain reaction (PCR).

In 1987, the National Institute of Child Health and Human Development provided support to two medical genetic centers to undertake a systematic approach to the study of the use of fetal cells obtained from maternal blood for prenatal diagnosis of genetic diseases. At present, the main focus of these investigators is to determine if fetal cells are actually present in the maternal peripheral circulation. There is little doubt that while trophoblast cells reach the maternal circulation, they are "deported" to the lungs, where they are

removed and prevented from remaining in the peripheral blood in significant numbers. One of the approaches, that of Adinolfi and his group at Guy's Hospital in London, illustrates the current disillusionment with the potential of prenatal diagnosis based on fetal cells present in the maternal circulation. Original reports in 1984 [6] and 1986 [7] suggested that using a monoclonal antibody that reacted with trophoblast, cells were recovered from peripheral blood which appeared morphologically as mononucleated or multinucleated trophoblast. However, the most recent report from the Adinolfi group [9] indicated that this interpretation was incorrect. Rather than fetal cells, in reality fetal antigen had been trapped by maternal monocytes. And, when the maternal monocytes trapped fetal antigen, they assumed the appearance of fetal cells in the maternal circulation.

One of the two NIH-supported groups working on the problem of detecting fetal cells in maternal blood believes that fetal cells are present in the ratio of 1 cell per million maternal cells and that techniques need to be developed which lead to the enrichment of this small pool of fetal cells. The focus of the two groups has been the use of FACS combined with PCR, in order to first enrich the pool of fetal cells, if present, and then to amplify their DNA for genetic analysis. But the promise of gene amplification of single cells by PCR is fraught with technical difficulties, particularly with laboratory contamination and the possibility of false-positive results. The issue remains unresolved at present. Are fetal cells, or at least DNA sequences, derived from the fetus present in the peripheral circulation of the mother during pregnancy? Is it possible to develop noninvasive, rapid and accurate techniques for use in the early prenatal diagnosis of human genetic diseases? The prospects for providing such an approach are exciting but the goals have yet to be achieved.

What Will Be Achieved in the 21st Century with Respect to Reproductive Genetics? Here Are My Predictions:

The year 2001 will be called the "Year of the Sperm." For the first time it will be possible to unequivocally separate X-bearing sperm from Y-bearing sperm in humans. This is not possible at the present time, despite numerous claims. But, by 2001, a technique will have been developed which uses monoclonal antibodies that selectively bind to either X-bearing or Y-bearing sperm and inactivates them. Thus, there will be an option to have the sex of one's offspring determined prior to implantation. This technique, selecting viable sperm on the basis of the presence of the X or Y chromosome, is likely to be very controversial. Could this technique lead to universal restrictions because its widespread use could very easily be directly responsible for changing the sex ratio in many societies?

If 2001 will be the "Year of the Sperm," then 2002 will be the "Year of the Egg." Earlier, in 1988, it appeared possible but technically difficult to

cryopreserve human oocytes and maintain their viability for future pregnancies. In 2002, I am predicting that a group of French reproductive endocrinologists (who else?) will develop a synthetic hormone which will cause the maturation of hundreds of follicles at the same time. Given these developments, it would be quite likely that certain government officials would demand regulation of egg banking practices. Given the large number of available donors, only women with certain mental and physical characteristics might be allowed to bank their eggs. Certainly, only women less than 35 years of age could donate their eggs for cryopreservation, to minimize the possibility of an advanced maternal-age related, chromosomally abnormal conception. There may be a group of professional women in the early part of their careers, in their 20s for example, who may wish to store a suitable number of oocytes to be retrieved later, when they are in their 30s, 40s or 50s, when their family is to begin, and when their professional lives are satisfactorily established.

By the year 2003, classic cytogenetic analysis will indeed be classical. Chromosomal analyses will be based on the use of chromosome-specific, fluorescent DNA probes. A "cocktail" approach will be used, in which it will be possible not only to determine chromosome number but also identification of specific trisomies, as well as structural rearrangements. Such analyses will be performed on cells in interphase; the entire process of harvesting, staining and evaluating such cells will be performed by combining the technologies of robotics, computers and recombinant DNA.

By 2005, Watson predicts that the human genome will be completely sequenced. This will lead to the following developments:

By the year 2010, if not earlier, gene therapy will be performed at the embryonic level, most likely by directed modification of abnormal gene mutations. As a result of developments in IVF, preimplantation diagnosis, and recombinant DNA technology, the methodology for germline gene therapy will have been perfected in the 1990s. The introduction of germline gene therapy will be preceded by extensive debate over legal, moral and ethical issues but the ability to cause positive, site-specific gene mutations, without altering any other genes in the complement, will eventually minimize these concerns. While individual families will benefit by this approach, the long-term goal of reducing the societal impact of familial mutant genes and chromosomal rearrangements will still be elusive.

The year is 2020. Everything is seen very clearly, of course, with respect to reproductive genetics. For, in the year 2020, a new device is developed, called a "gene scanner." This device will permit the entire scanning of the human genome, from chromosome 1 through 22 and the X and Y chromosomes, in order to ensure that there are no gene mutations causing serious health impairment. Gene scanners will eventually be applied to individual gametes as well as specific somatic tissues, eye, kidney, bladder, etc. If mutations have

arisen de novo, appropriate gene therapy could be applied before the clinical expression of the gene mutation occurs.

In the year 2050, artificial wombs will have been perfected and will be used by women who for a variety of reasons cannot carry a pregnancy to term. The implications are rather obvious. For example, man will begin to explore beyond the solar system using the technology of reproductive genetics. Since planets beyond the solar system may be many light years away, it is not "inconceivable" that oocytes and sperm will be cryopreserved, placed on rocket ships, sent into space and at predetermined times, different lots of oocytes and sperm will be thawed, fertilized and developed in artificial wombs. Childrearing practices on rocket ships have yet to be fully developed but given NASA's recent history with the Hubble telescope, is there any reason not to trust their judgment in the 21st century?

Aldous Huxley observed that "the purpose of science is to understand nature and then to control it." In that sense, reproductive genetics epitomizes this belief but carries with it certain obvious responsibilities. How does one apply the mechanistic approach of science—in vitro fertilization, sperm and egg banks, artificial wombs—and yet maintain one's humanness? That may be the most significant issue upon entering the 21st century.

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Low MSAFP and New Biochemical Markers for Down Syndrome: Implications for Genetic Counselors

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The prenatal detection of birth defects, having been available for over 20 years, is sometimes referred to as "routine." This may be true especially when referring to amniocentesis for advanced maternal age (AMA), or elevated maternal serum alpha-fetoprotein (MSAFP). While many veteran genetic counselors have witnessed the evolution of some testing modalities from "experimental" to "routine," a relatively small number of their clients are likely to describe their personal experience with prenatal diagnosis as "routine."

Even something as commonly used and clinically benign as MSAFP screening, while rapidly becoming routine, is at the same time becoming more demanding as new applications are found. A technology which ten years ago was considered to be useful only for detection of open neural tube defects (ONTD) is now being enhanced to identify the majority of cases of fetal Down syndrome (DS), requiring a major change in the way that genetic counselors, physicians, and pregnant women view DS detection.

This new approach to DS screening will impact significantly on the profession of genetic counseling. In order to appreciate the distinction between the "traditional" way of testing for DS and the approach that is sure to become "routine" within the next several years, it is important to examine how DS testing has evolved.

FIRST GENERATION DS SCREENING

For 50 years it has been recognized that there is a significant positive association between increasing maternal age and increasing birth prevalence of Down syndrome [1]. While the exact mechanism accounting for this correlation has not been identified, the risk of having a child with DS—or for several other chromosomal disorders—remains a significant concern to older women.

When amniocentesis became available as a relatively safe means to remove fluid and fetal cells for accurate karyotyping during the midtrimester of

pregnancy, theoretically every case of fetal DS could be prenatally diagnosed. However, this was obviously impractical for several reasons: facilities did not exist to analyze the amniotic fluids from the three million pregnancies annually in this country; there were few clinicians trained to perform amniocentesis; financial costs were significant; and even if there were enough facilities, technicians, and money available to test every pregnancy, it was unlikely that every pregnant woman would undergo a procedure that carried a reported risk of pregnancy loss of about 1 in 200 [2]. If this technology were to have an impact on reducing the birth prevalence of DS, an approach would need to be implemented that would not overburden resources and which would have a favorable cost-benefit ratio.

Since there were sufficient data to ascribe risk of delivering an infant with DS with maternal age, it made sense to use this information to construct a protocol that focused on risk as variable. Examination of curves demonstrating this relationship suggests that the risk of DS increases steeply after the age of 31 or 32 (Fig. 1). Offering women diagnostic testing before this age would seem to be inefficient. Examining the distribution curves for DS and unaffected pregnancies as a function of maternal age is helpful as well: while the mean age of women bearing DS infants is about 31 years, the difference between the distributions at age 31 is minimal (Fig. 2). Only around age 35 or higher does the relationship between the height of the curves suggest at least a two- or threefold increase in risk between the two populations. Coupled with the knowledge that at age 35 or above the prevalence of other chromosomal aneuploidies was approximately equal to the risk of DS [3], and that cost-benefit calculations for prenatal diagnosis were favorable at age 35 [4], it became standard practice to offer diagnostic testing for women age 35 or older.

While not characterized as such, offering amniocentesis to women at or above the age of 35 (or any other preselected age) was a form of screening. In this case the test was a simple one, the mere asking of a question ("What is your date of birth?" or similar variant). The test "results" were "interpreted," and if the results were above the determined cut-off (eg, 35), the patient tested positive ("screen positive") and was a candidate for a confirmatory test, namely fetal chromosome analysis.

The screening was reasonably sensitive: maternal age screening (using a cutoff of $\geq 1:385$) has a sensitivity of 20–25% with a specificity of 95% (ie, 5% false-positive rate). However, because of the low prevalence of Down syndrome, only 1 in 140 (Fig. 3) or so screen positive tests would be associated with an affected pregnancy. But this screening was able to identify a population whose risk associated with fetal DS was four or five times greater than that of the general population.

Despite increasing evidence that amniocentesis was becoming safer, the

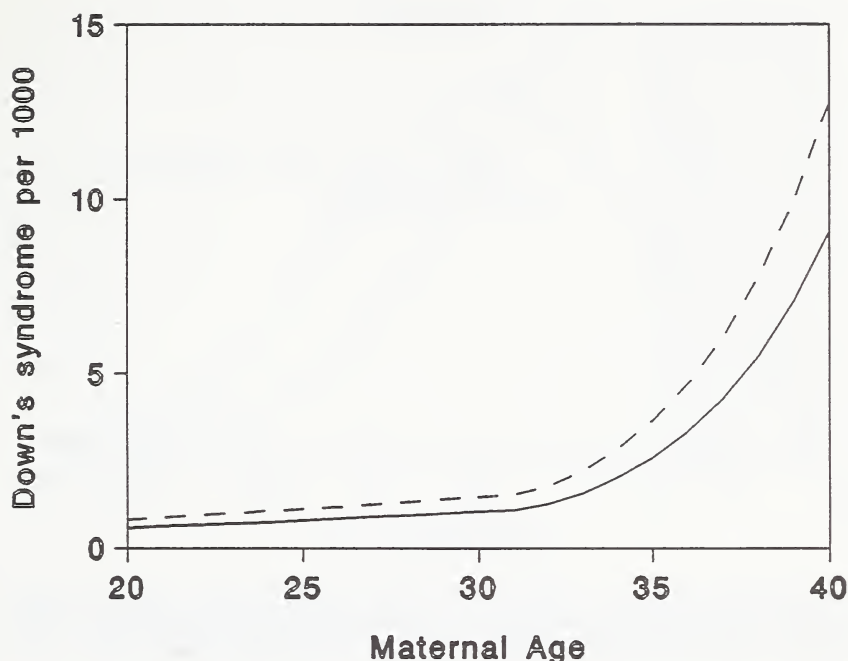


Fig. 1. Rate of Down syndrome vs maternal age in the second trimester (dotted line) and at birth (solid line). The lower risk of delivering a Down syndrome baby vs carrying a Down syndrome fetus is a consequence of the estimated 29% loss rate in the third trimester. (From Clin Obstet Gynaecol, Vol. 31, No. 2, p 307, June, 1988, with permission).

overall utilization of this testing was relatively low, with less than half of women over the age of 35 taking advantage of prenatal testing [5, 6].

While not universally accepted, amniocentesis was used or at least offered often enough to stress the health care system. In 1979, approximately 65% of amniocenteses were performed with AMA as the indication. The NIH Task Force on Predictors of Hereditary Disease of Congenital Defects reported that year that as the utilization of amniocentesis increased, more trained genetic counselors would be needed to provide their professional services [7]. That report was released the same year that genetic counselors organized themselves as the National Society of Genetic Counselors, whose tenth anniversary is celebrated in this volume.

This first generation screening test was capable of detecting, at best, one out of four affected fetuses—the remaining three would be carried by women under the age of 35 (screen negative) and would not be candidates for further testing. Any enhancement of this first generation screening test would need to

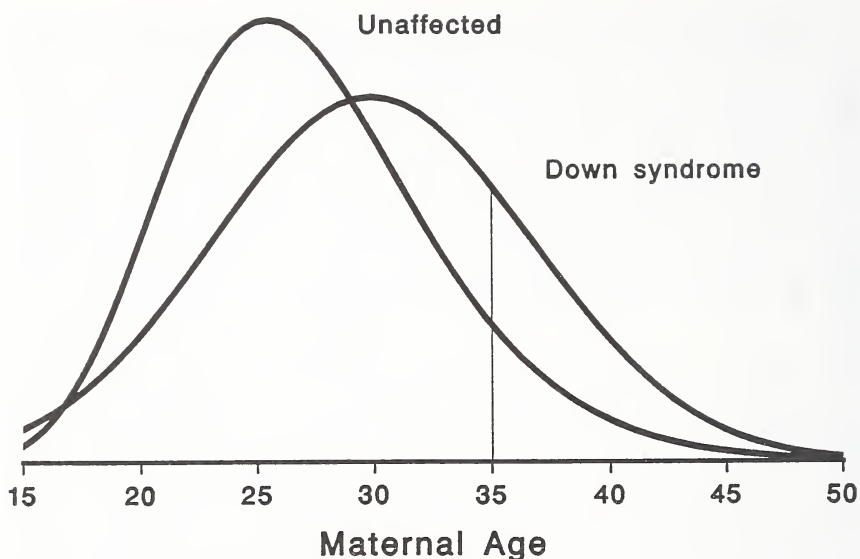


Fig. 2. Distribution of maternal age associated with Down syndrome and unaffected pregnancies. Vertical line at age 35 indicates that at this age, risk of Down syndrome is approximately twice as high as background risk.

rely on a variable other than maternal age, and if it were going to provide any significant improvement in DS detection rates, would need to be essentially independent of maternal age.

SECOND GENERATION DS SCREENING: MATERNAL SERUM ALPHA-FETOPROTEIN (MSAFP)

The observation that low MSAFP levels were associated with fetal trisomy, reported in 1984 by Merkatz et al [8], provided the basis for developing a better DS screening approach. Following this report, Cuckle and Wald [9] analyzed the results of 66 pregnancies with fetal DS, confirming the observations of Merkatz. They determined that the median MSAFP multiple of the median (MoM) in the affected population was 0.72, significantly lower than the value of 1.00 in the unaffected population. More importantly, maternal age and MSAFP levels were independent predictors of DS risk. Confirmed since then by several studies, this observation allowed access to DS screening to the 95% of pregnant women who are under 35 and therefore not candidates for amniocentesis on the basis of age alone.

The association between low MSAFP levels and risk of DS can be used alone to assign risk to all pregnant women, independent of maternal age. An

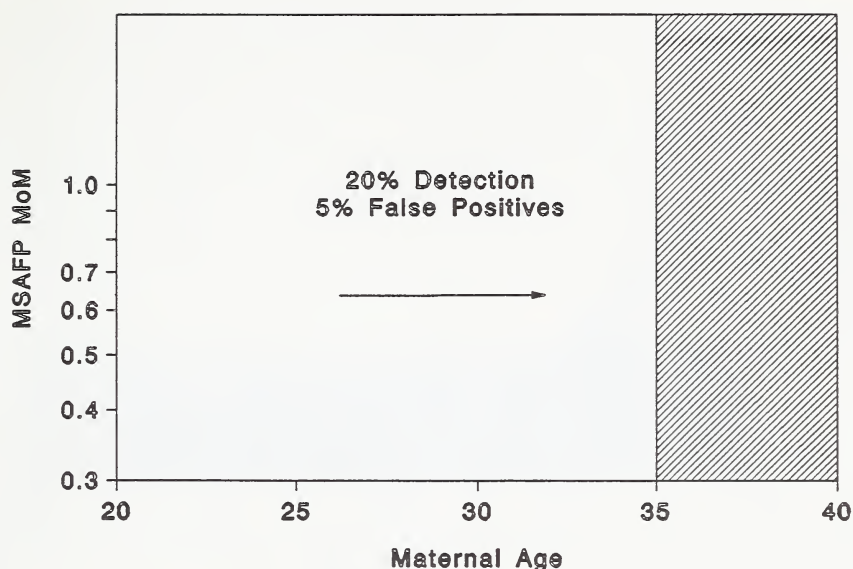


Fig. 3. Women at increased risk for carrying a Down syndrome fetus (hatched areas) as defined by maternal age \geq age 35 years. (Figs. 3–5 from *Clin Obstet Gynecol*, Vol. 31, No. 2, p 308, June, 1988, with permission.)

MSAFP cut-off could be selected, 0.5 MoM for example, at or below which any woman would be screen-positive (Fig. 4). The selection of 0.5 MoM would result in about 5% of women being called positive regardless of age, and subsequent amniocentesis and karyotyping would identify 20% of affected pregnancies—no improvement over using maternal age alone. However, to utilize MSAFP alone, ignoring the spectrum of a priori risk determined by maternal age, would lose the advantage found by combining the power of both tests. Each a priori risk assigned to maternal age can be modified by the risk associated with MSAFP to create a patient-specific posteriori risk: younger women with low MSAFP levels may have risks similar to older women with higher MSAFP levels. This approach could detect nearly 40% of DS fetuses, at a screen-positive rate of 7–8% (Fig. 5).

The impact of this second generation DS screening on genetic counselors was significant and immediate:

- Physicians were being asked to modify a familiar standard of care which dictated that increased risk of DS was experienced only by women over 35. Programs that incorporated MSAFP screening for DS needed to provide extensive physician education regarding risk assignment.
- Younger women who were screen-positive needed immediate counseling regarding DS risk. They were not expected to have given much thought to

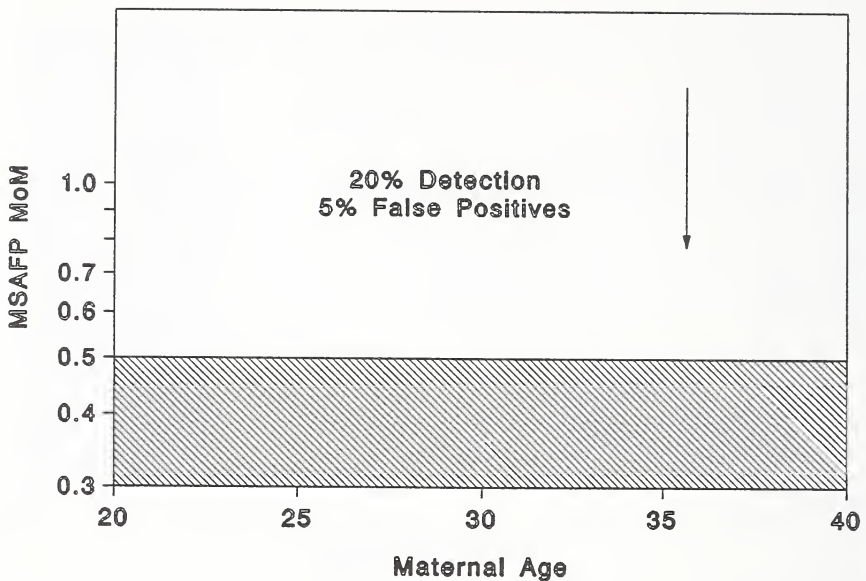


Fig. 4. Women at increased risk for carrying a Down syndrome fetus (hatched areas) as defined by MSAFP MoM less than 0.5.

a chromosomal abnormality generally associated with pregnancies in older women.

- As in screening for NTDs, DS screening protocols required ultrasound confirmation of gestational dates (as many as one half of screen-positive women may have overestimated dates) but, unlike NTD screening, repeat sampling is not recommended.
- Unlike screening for NTDs, there are no other generally reliable noninvasive tests to help confirm or rule out DS. Elevated MSAFP levels make use of repeat MSAFP testing, and ultrasound can help to identify or rule out some NTDs. Once a modified DS risk is established, however, the only available diagnostic follow-up test involves amniocentesis and karyotype.
- MSAFP assays had been designed to perform optimally at levels useful to NTD detection. Usage of test kits without initially assessing their low level performance, could lead to inaccuracies in risk assessment for DS [10].
- Counselors should be aware of the potential differences in the parameters used by laboratories serving their patient population. For example, women at a given age with similar MSAFP concentrations may be assigned different individual risks depending on the data used to con-

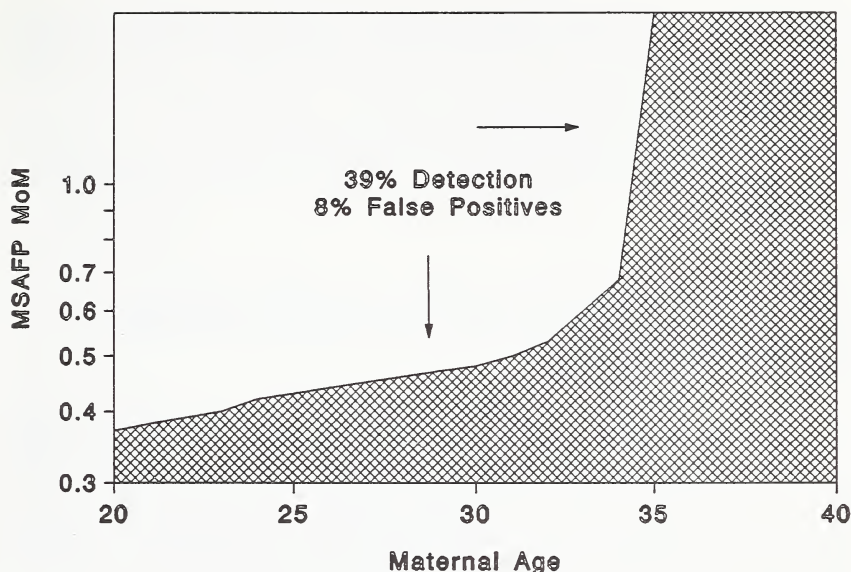


Fig. 5. Women at increased risk for carrying a Down syndrome fetus (hatched areas) as defined by a combination of MSAFP and maternal age to identify women with risk equal to or greater than that of a 35-year-old woman.

construct the age-risk table, whether the DS risks are calculated for mid-trimester or for term, and whether the risk assigned to a given MoM is specific to that MoM or whether it includes cumulative MSAFP values at or above that MoM. Additionally, failure to adjust for maternal weight will result in an inappropriate number of heavy women being assigned lower MSAFP MoMs (and consequently a higher DS risk) [12].

Minimizing the potential problems encountered with second generation DS screening requires that the counselor spend a considerable time playing the role of educator. Prenatal care providers, their staff, program staff, clients, and the general public need repeated explanations regarding the application of MSAFP as a screening tool for DS.

One concept in particular needs to be introduced early and continuously in programs utilizing DS screening at any level—the concept of iso-risk [13]. A potential obstacle to second generation DS screening may be the resistance by patients and prenatal caregivers to abandon the benchmark of age 35 as the cut-off point for offering amniocentesis. Maternal age is simply another marker for DS risk. Thirty-five was selected as a cut-off point for amniocentesis because it corresponds with a risk of about 1 in 270 and produced a reasonable false-positive rate. It is the risk, not the age, that is the true

reference point in decision making. Any device or test that can help to identify risk of DS can be incorporated into the screening protocol. Therefore, any combination of maternal age and MSAFP, which corresponds to risk of 1 in 270 for DS, will yield an iso-risk of 1 in 270. A 27-year-old woman with a MSAFP level of .45 MoM will have a risk equivalent to a 35-year-old woman (who has not had a MSAFP test). The risk becomes important, the age only a component.

THIRD GENERATION DS SCREENING: MATERNAL SERUM UNCONJUGATED ESTRIOL (MSUE₃) AND HUMAN CHORIONIC GONADOTROPIN (MShCG)

The suspicion that the decreased level of MSAFP associated with DS may be due to a decreased fetal synthesis or processing of MSAFP was heightened by the observation that amniotic fluid as well as cord blood MSAFP levels were also significantly lower in association with DS [14]. If a dysfunctional fetal liver or placenta was responsible for the decrease in MSAFP, perhaps there were other biochemical markers whose concentrations in maternal serum were also affected.

Two independent reports in 1987 ushered in the third generation of DS screening. Canick and others [15] reported that MSuE₃ levels were significantly lower in DS pregnancies. Meanwhile, Bogart et al [16] reported that MShCG was elevated in DS pregnancies.

MSAFP, MSuE₃, and MShCG were relatively independent markers, allowing them to be used to enhance the detection rate of fetal DS.

Wald et al [17] demonstrated that, using MSuE₃ with MSAFP and age, about 45% of DS fetuses could be detected following amniocentesis on about 5% of women. Substituting MShCG for estriol detected 55% of DS fetuses at the same amnio rate. But using age, MSAFP, estriol and MShCG would result in 60% of DS fetuses being detectable following amniocentesis on 5% of the pregnant population.

Currently, several laboratories offer DS screening using MSAFP and at least one other of these two biochemical markers. While other biochemicals—S 100 β , human placental lactogen, SP₁, etc—have been or are currently being investigated, it is likely that for the time being MSAFP, MSuE₃, and MShCG will receive the attention of DS screening programs.

These three markers are similar in that they are normally present in both DS and unaffected pregnancies and that they are not specific for DS. The implications that this screening will have on genetic counseling are therefore valid regardless of whether MShCG alone or MShCG plus MSuE₃ are used. The improvement in detection capabilities using various combinations of screening markers at similar screen-positive rates is summarized in Table 1.

TABLE 1. DS Detection Rates With Various Combinations of Markers (Screen-Positive Rate Fixed at ~5% for Comparison Purposes)

Marker(s) Used	Detection Rate (%)	Screen-Positive Rate (%)
Age	25	5.0
Age and MSAFP	35	5.3
Age and MSuE ₃	40	5.0
Age and MSAFP and MSuE ₃	45	5.3
Age and MShCG	50	5.4
Age and MSAFP and MShCG	55	5.0
Age and MSuE ₃ and MShCG	55	4.4
Age and MSAFP and MSuE ₃ and MShCG	60	4.7

IMPLICATIONS FOR GENETIC COUNSELORS

The Counselor's Relationship With the Patient

As DS triple marker screening becomes routine, counselors will be forced to spend increasing amounts of time with clients. Approximately one out of every 15 women will be screened positive for DS. These women will be candidates for ultrasound and/or amniocentesis, and time will be of the essence. If these women and their partners have not been adequately informed prior to screening of the significance of being screened positive, there will be a need for the physician's office or screening program to initiate counseling. In order to complete ultrasound and/or amniocentesis and appropriate chromosome analysis, there will be little time available for any delays.

Ideally, pregnant women will have been informed prior to screening, and will understand the relationships between the levels of biochemical markers and their risk of DS. This can be accomplished best by the use of clearly written and appropriately targeted pamphlets, and graphics, easily understood videotapes, and opportunities for discussion with professionals.

In a few cases, there will be older women whose risk for DS has decreased as a result of marker analysis. These women may have been prepared already for amniocentesis and may not be willing to believe that their risk has changed significantly. Only 20–30% of women 35 or older would be candidates for amniocentesis following triple marker testing; however, the detection rate of DS would also decrease from 100% to 90% in this group.

Chromosomal aneuploidies other than trisomy 21 are not expected to be assigned high DS risk estimates [18]. Counselors will need to avoid giving false assurances to older women who are not screen-positive for DS—their risks of other aneuploidies are not diminished.

Physicians will need to consider that neither the Food and Drug Administration nor American College of Obstetricians and Gynecologists has approved the use of MShCG or MSuE₃ for DS identification. The degree to which the

use of these markers dictates standard of care will probably be determined within each community.

Physicians will need to be discouraged from using these markers as a confirmatory screening test, ie, sending repeat samples on women who screen-positive on MSAFP testing to a laboratory offering additional markers. The interpretation of such samples is different and such a policy would result in a loss of DS detection and could provide false assurance to many women [11].

Counselors will also need to assure physicians that the changes in DS risk observed when a gestational age is corrected are accurate, though dramatic (Table 2). Ultrasound dating prior to sample drawing will reduce the number of screen positives and reduce the need for reassignment of risk.

Many physicians have become proficient in examining an MSAFP MoM along with a patient's age, and determining whether her DS risk should be higher or lower than her age-related risk. The use of the new markers will make such an exercise extremely difficult. A woman with a low MSAFP may have a high enough estriol and low enough MShCG to reduce her DS risk several-fold. This may not be readily apparent even to the experienced observer. The physician will need to trust the calculation used to derive the risk estimate. A total of 21 separate pieces of information are needed to calculate a DS risk using the two new markers. This cannot be done manually by the average clinical laboratory. Software programs designed to integrate laboratory, clinical, and patient demographic information will be a necessary component in any serious third-generation screening effort [12].

Thought needs to be given to how risks will be presented. An individual's risk for DS may double or triple—but still be below the screening cutoff. How will the physician and patient react?

The Counselor's Relationship With the Policy Makers

In establishing a screening program using new markers, several parameters need to be determined. The program may decide to target a specific DS

TABLE 2. Effect of Incorrect Gestational Dating on Second Trimester DS Risk (Maternal Age = 32)

Markers Used	Risk at Reported Gestational Age Of 17 Weeks	Risk at Corrected Gestational Age Of 15 Weeks
Age	1:485	1:485
Age and MSAFP	1:240	1:344
Age and MSAFP and MSuE ₃	1:240	1:1,420
Age and MSAFP and MSuE ₃ and MShCG	1:240	1:2,555

As the number of markers used for DS screening increases, so does the impact of incorrect gestational dating. In this example, a 32-year-old woman thought to be two weeks further along than she actually is has her DS risk changed much more significantly as the number of markers used to determine DS risk increases.

detection rate, screen-positive rate, or risk cutoff. Fixing one of these three parameters will determine the remaining two. Counselors should be involved in the selection of these parameters, since these three variables may become part of both a physician educational effort as well as individual patient counseling. The actual performance of the screening program will be determined by factors including the percent of women in the screened population older than 35, the percent of screened women whose dates are confirmed by ultrasound prior to screening, and the attitude toward and availability of pregnancy termination within the community.

Counselors should also be aware that third-generation screening could increase biochemical and cytogenetic laboratory revenues as well as increase ultrasound and counseling referrals. The impact on the health care system, including reimbursement issues, has not been adequately addressed.

ACTION ITEMS FOR GENETIC COUNSELORS

- 1) Become involved with education.
Besides informing yourself about the implications of third-generation DS screening, become active in educating prenatal care providers, patients, and the public.
- 2) Learn what screening parameters are used. It is not necessary that a genetic counselor involved with a DS screening program be a proficient laboratorian. However, he/she should be aware of the type of assay used and the proficiency of the laboratory. In addition, the counselor should be satisfied that the risk table and algorithm used are accepted by the screening community.
- 3) Begin to think in terms of risk assessment.
There should be a de-emphasis on using age as *the* indication of risk. It should be regarded as simply one of three or four indicators of risk, and not a particularly impressive one.
- 4) Be aware of the implications for older women.
This screening is not meant to replace amniocentesis in women who have a significant risk of other chromosomal aneuploidies. Older women who utilize the testing to get a better estimate of their risk for DS should be aware that this testing is not designed to screen for other chromosomal aneuploidies.
- 5) Be prepared to respond to numerous questions.
The introduction of third-generation screening in a community will require added genetic counseling resources as prenatal care providers and patients adjust to this new approach.
- 6) Become involved in policy decisions.
Counselors may need to defend the selection of screening program

parameters, and their workload will be influenced by the screen-positive rate.

7) Initiate and publish research on counseling issues.

While the literature is replete with information on assay performance, statistical and epidemiologic data, and program experience, there are relatively few references to counseling issues. Counselors should endeavor to investigate the effect of different approaches to information presentation, follow-up counseling, and patient perception of risk. Opportunities abound for genetic counselors to make major contributions to this growing field.

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Assessment of Routine Amniocentesis for Unexplained Maternal Serum Alpha-Fetoprotein Elevations

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INTRODUCTION

With a frequency of one to two per 1,000 live births, neural tube defects are one of the most common congenital malformations occurring in the United States [1]. It has been estimated that 85% of all neural tube defects can be identified by maternal serum alpha-fetoprotein (MSAFP) screening [2, 3]. Since 90–95% of neural tube defects occur in families with no previous neural tube defect history, effective neural tube defect screening should involve all pregnancies. The introduction of the MSAFP screening test is significant in obstetric care for it provides a simple, noninvasive method of identifying the majority of women who are carrying a fetus with a neural tube defect, and thus may benefit from diagnostic testing.

When a fetus is affected with an open neural tube or other open defect, increased levels of AFP enter the amniotic fluid by diffusion from cerebral spinal fluid or fetal circulation. Although MSAFP began as a screening tool for neural tube defects, it is apparent that elevated MSAFP is also helpful in identifying pregnancies at increased risk for many other unfavorable outcomes such as miscarriage, stillbirth, low birthweight (LBW), or other fetal abnormalities [3–6].

Richards et al [7] reported that after ultrasound was used to exclude women for incorrect dates, multiple gestation, and fetal death, only 5% of the remaining elevated MSAFP patients actually had a fetus with a neural tube defect. Currently, most screening programs counsel their patients to undergo amniocentesis when ultrasound cannot explain an elevated MSAFP value. Since diagnostic ultrasound cannot presently detect 100% of open spinal defects, Drugan et al [8] suggested that amniocentesis should be considered an essential part of the diagnostic workup for all women with unexplained MSAFP elevations. One screening program has reported adjusting the esti-

mated probability of a pregnancy being affected by a neural tube defect if a woman with an elevated MSAFP value has a normal ultrasound exam [7]. The adjustment is based on an approximate detection sensitivity of 100% for anencephaly and 80% sensitivity for open spina bifida with diagnostic ultrasound. Since spina bifida and anencephaly each make up approximately half of neural tube defect cases, the combined sensitivity of ultrasound for open neural tube defects was estimated to be 90%. Some women with only slightly elevated MSAFP values may have an adjusted risk for a neural tube defect lower than that of the general population after a normal ultrasound.

This study investigated pregnancy outcome in women with unexplained MSAFP elevations who had amniocentesis, and the effect of using ultrasound-reduced risk estimates for open spina bifida to determine if amniocentesis could be avoided without significantly reducing neural tube defect detection.

MATERIALS AND METHODS

The study population consisted of all women who had an amniocentesis at the University of South Carolina School of Medicine with the indication of elevated maternal serum alpha-fetoprotein during the years 1986–1988.

MSAFP values for private and health department patients were reported as risk estimates by Neural Tube Defect Laboratories from January, 1986 to December, 1986. Multiples of the median were calculated for other private and health department patients between August, 1986 and December, 1988. Serum samples from private patients were analyzed by Palmetto Pathology Services using Abbott polyclonal or Hybritech monoclonal reagents. Serum samples from health department patients were analyzed by South Carolina Department of Health and Environmental Control Bureau of Laboratories using Kallestad reagents from August, 1986 to June, 1988, and Hybritech monoclonal reagents from July, 1988 to December, 1988. Interpretations for all MSAFP tests, except those reported by Neural Tube Defect Laboratories, were performed by the University of South Carolina School of Medicine, Department of Obstetrics and Gynecology, Division of Clinical Genetics.

Information collected from existing patient records for each individual in the study group included maternal age, race, weight, presence of insulin-dependent diabetes mellitus, family history of neural tube defect(s), amniotic fluid alpha-fetoprotein (AFP) value, maternal serum alpha-fetoprotein (MSAFP) value, gestational age at MSAFP and amniocentesis, fetal chromosomal constitution and acetylcholinesterase pattern. Furthermore, ultrasound clarity, anomalies observed, and estimated date of confinement (EDC) were recorded.

The outcome of all pregnancies with unexplained MSAFP elevations was

also investigated from patient records including birthweight, date of delivery, congenital anomalies, placental anomalies, miscarriages, and stillbirths. The data were compiled for comparison with expected values from the general population.

Transabdominal and transvaginal ultrasound exams were performed using Adratl's Model 4000 or Ultramark 4 with either a 3.5 or 5 mHz transducer. The quality of the ultrasound scans were judged by one of two MD ultrasonographers as being "good," "fair," or "poor." The length of gestation of each pregnancy at delivery was determined by comparing the ultrasound EDC at the time of amniocentesis with the actual delivery date. Ultrasound EDCs are accurate to ± 7 days in 95% of cases when using biparietal diameter measurements prior to 20 weeks gestation [9].

Low birthweight (LBW) was defined as a weight of <2.5 kg at delivery. Small for gestational age (SGA) was used to denote a weight below the 10th percentile for gestational age. A weight above the 90th percentile was considered large for gestational age (LGA). A chart of birthweight standards for males and females based on early ultrasound estimate of gestational age was used to classify pregnancies in the study group [10].

The current protocol for all pregnancies with elevated MSAFP values, which are unexplained by diagnostic ultrasound, is to recommend amniocentesis for further study. This was the protocol employed in the study group. The alternate theoretic protocol investigated involved calculating each pregnancy's risk for open spina bifida based on the most recent MSAFP MOM, then reducing this risk by 80% in pregnancies with a "good" quality ultrasound scan (as defined by the ultrasonographers) revealing no anomalies. A detection rate of 100% was presumed for anencephaly. Women with a revised estimate lower than 1/200 would not be recommended for the amniocentesis procedure. Thus, two groups have been delineated: those who would not have had an amniocentesis based on their revised risk and those who would have had the procedure regardless. Calculations of likelihood for open spina bifida were made from the log-Gaussian distribution using Bayesian analysis [11]:

The a priori risks of spina bifida used for different groupings of patients based on their race and diabetes mellitus status from South Carolina Hospital discharge data are: black (not insulin-dependent) = 1/3333; white (not insulin-dependent) = 1/1250; black insulin-dependent = 1/665; white insulin-dependent = 1/332.

The proportion of chromosomally abnormal newborns, fetal wastage (stillbirths and miscarriages) following amniocentesis, birthweights < 2500 gm, gestational ages < 37 weeks at delivery, fetuses small or large for gestational age, placenta previas, and abruptio placentas were evaluated for significance by the Distribution of Sample Proportion analysis [12].

RESULTS

Between January, 1986 and December, 1988, amniocentesis was performed on 188 pregnancies at the University of South Carolina School of Medicine for MSAFP elevations. Twenty-seven cases were excluded from the study due to multiple gestation, family history of neural tube defect(s), or lack of MSAFP data. A total of 161 pregnancies were included in the analysis.

The majority of ultrasound scans (115/145) performed at the time of amniocentesis were judged to be of "good" quality. Abnormalities in the quantity of amniotic fluid or in the fetus were documented on ultrasound in 7% (10/145) of the study group. Abnormalities detected by diagnostic ultrasound included two cases of oligohydramnios, two cases of fetal hydrocephaly, two cases of open spina bifida, two cases of omphalocele, one case of gastroschisis, and one case with gastrointestinal and genitourinary anomalies.

When considering only those pregnancies with "good" quality scans, abnormalities were noted in 5.2%. Therefore, the percentage of anomalies noted on good quality scans was approximately the same as that noted on all scans, regardless of quality.

Amniocentesis results included acetylcholinesterase pattern, amniotic fluid AFP concentration, and chromosome constitution. Using 2.0 multiples of the median as a cutoff for normal amniotic fluid AFP values, AFP was elevated in 11 pregnancies, acetylcholinesterase patterns were positive in 8 pregnancies (Table 1), and chromosomal abnormalities were noted in 3 pregnancies. The chromosomal abnormalities that were found included: 69,XXX; 47,XYY; and 46,XY,inv(6)(p12q23). The triploid pregnancy in this study miscarried at 23 weeks gestation before chromosomal studies were completed. Both the 47,XYY and 46,XY,inv(6)(p12q23) pregnancies were continued and resulted in live births with no major physical abnormalities. Thus, chromosomal anomalies were present in 1.7% (2/120) of live births with elevated MSAFP values.

In the 109 pregnancies that a "good" quality diagnostic ultrasound revealed no abnormalities, amniocentesis results revealed 2 with positive acetylcholinesterase, 4 with elevated amniotic fluid AFP, and 2 with chromosomal abnormal-

TABLE 1. Results of Amniocentesis: Acetylcholinesterase (ACHE) Patterns and AFAFP Values in Pregnancies With Unexplained MSAFP Elevations

Test Result	ACHE		AFAFP	
	Number	Percent	Number	Percent
Positive	8	5%	11	7%
Negative	148	92%	147	91%
Inconclusive	2	1%	—	—
Not performed	3	2%	3	2%
Total	161	100%	161	100%

ities. However, there were 6 pregnancies (5.5%) where amniocentesis indicated an abnormality when good quality diagnostic ultrasound failed to do so (Table 2). The outcomes of the six pregnancies, in which amniocentesis results indicated an abnormality not observed with "good quality ultrasound, are described in Table 3.

None of the four pregnancies with positive acetylcholinesterase patterns and/or amniotic fluid AFP values were affected with a neural tube defect or ventral wall defect.

The only anomalies that would not have been detected using the altered protocol were the two chromosomal anomalies detected by amniocentesis: 47,XYY; and 47,XY,inv(6)(p12q23). Using the altered protocol, amniocentesis would have been indicated in all pregnancies shown to be positive for acetylcholinesterase or with elevated amniotic fluid AFP, and no open neural tube defects or ventral wall defects would have been missed.

Reducing the risk of open spina bifida by 80% when patients had a "good" quality diagnostic ultrasound revealing no abnormalities, 40% (65/161) of amniocenteses could have been avoided using a 1/200 risk cutoff. Interestingly, using a MSAFP-derived risk for open spina bifida without consideration of ultrasound and a 1/200 risk cutoff for amniocentesis, 11.2% (18/161) of the amniocenteses could have been avoided.

Birth information was available for 86.3% (139/161) of pregnancies. Pregnancy outcomes were classified as live births, therapeutic terminations, and fetal losses. Eighty-six percent (120/139) of pregnancies resulted in live births. Therapeutic terminations were performed in three pregnancies in which open spina bifida was prenatally diagnosed. Fetal loss is used to denote all miscarriages, intrauterine fetal deaths, and stillbirths. Twelve percent (16/139) of pregnancies resulted in fetal loss. This represents a significantly higher loss rate in the study population in comparison with the 3.5% expected loss rate following amniocentesis for reasons other than an elevated MSAFP value [13] ($t = 5.13$, $p < 0.0001$). All adverse outcomes including fetal loss

TABLE 2. Pregnancies in Which Amniocentesis Results Indicated an Abnormality Not Observed With "Good" Quality Diagnostic Ultrasound Alone. Risk of Open Spina Bifida Calculated From MSAFP Value

Case	MSAFP MOM	AFAPF	ACHE	Karyotype	Risk of Spina Bifida
1	10.10	Elevated	Negative	Normal female	1/5
2	6.80	Elevated	Negative	Normal male	1/5
3	4.63	Elevated	Positive	Normal male	1/10
4	7.50	Elevated	Positive	Normal female	1/5
5	2.60	Normal	Negative	47,XYY	1/1084
6	2.80	Normal	Negative	46,XY,inv(6)(p12q23)	1/644

TABLE 3. Outcomes of Pregnancies in Which Amniocentesis Results Indicated Elevated AFAFP, Positive ACHE Pattern, or an Abnormality Not Observed With "Good" Quality Diagnostic Ultrasound Alone (Refer To Table 2 For Predelivery Data)

Case	Weeks Gestation at Delivery	Anomalies
1	38	None
2	29	Amniotic band complex: amputation of lower leg, multiple digits on hands
3	22	Cord stricture; intrauterine fetal death
4	18	Placental infarcts; intrauterine fetal death
5	39	None
6	39	Facial hemangioma

and therapeutic terminations totaled 13.75% (19/139) of all pregnancy outcomes.

Anomalies documented at delivery were classified as those seen in live births, fetal losses, or therapeutic terminations (Table 4). Major malformations were observed in 4.3% (5/117) of live births to non-insulin dependent (non-IDDM) women in the study group. This represents a significantly increased percentage of major malformations in live births to non-IDDM women in the study group when compared to non-IDDM women in the population ($t = 3.79$, $p = 0.0001$).

Major malformations found in fetal losses due to miscarriages and stillbirths amounted to 13% (2/16). The study group had a significantly increased rate of malformations found in fetal losses in comparison to the general population ($t = 2.23$, $p = 0.0129$).

The types of major malformations found in live births, fetal losses, and therapeutic terminations are listed in Table 5. Two anomalies documented in two live births were not included as they were not classified as major

TABLE 4. Major Malformations Reported At Delivery In Live Births, Fetal Losses, and Therapeutic Terminations in Women With MSAFP Elevations (Ratio of Anomalies: Numerator Is The Number of Pregnancies With Anomalies; Denominator Is The Number of Pregnancies Included In The Category)

Pregnancy Result	Ratio of Anomalies	Percent
Live births	(5/120)	4
Fetal losses*	(2/16)	13**
Therapeutic terminations†	(3/3)	100
Total	(10/139)	7

*Includes miscarriages and stillbirths.

** $p = 0.0001$.

†Pregnancy terminations; prenatally diagnosed open spina bifida.

TABLE 5. Types of Major Malformations Reported at Delivery in Live Births, Fetal Losses, and Therapeutic Terminations in Women With Unexplained MSAFP Elevations

Pregnancy Result	Malformation Type	MSAFP MOM
Live births	Omphalocele*†	10.65
	Gastroschisis†, ventral septal defect	7.70
	Amniotic band complex: amputation of lower leg, multiple digits on hands	6.80
	Potter syndrome#	2.87
	Ambiguous genitalia, imperforate anus, bilateral thumb abnormality	2.50
	Malrotation of intestines, hypermobile joints, loose skin	3.50
Fetal losses‡	Multiple—unspecified	3.87
	Lumbar meningomyelocele, hydrocephaly	4.42
Therapeutic terminations**	Lumbosacral meningomyelocele	7.20
	Open spina bifida, ventriculomegaly, hematoma on buttocks	5.27

*Died at two months of age.

#Heart and kidney abnormalities, died at one day of age.

†Ventral wall defects were detected on diagnostic ultrasound and confirmed by amniocentesis, acetylcholinesterase patterns and AFAFP values; patients electively continued pregnancies.

‡Includes miscarriages and stillbirths.

**Pregnancy termination; prenatally diagnosed open spina bifida.

malformations. One infant had a large facial hemangioma; the other exhibited paralysis of the left arm.

The condition of fetal membranes was reported in slightly over half (85/161) of the study group (Table 6). Fetal membrane information was unavailable for many pregnancies as South Carolina Health Departments do not record such information routinely at delivery. Therefore, the 85 reports obtained represent those patients who received obstetric care from private physicians. Placenta previa was documented in 1.2% of pregnancies in the

TABLE 6. Anomalies Documented in Fetal Membranes in Women With Unexplained MSAFP Elevations

Anomaly Types	Number	Percent
Abruptio placenta	5	6*
Acute chorioamnionitis	3	4
Amniotic band complex	1	1
Cord stricture	1	1
Placenta previa	1	1 ^{ns}
Premature membrane rupture	1	1

* $p < 0.0001$.

ns = $p = 0.1210$, not significant.

study group, which is not significantly greater than the population incidence ($t = 1.17$, $p = 0.1210$). Abruptio placenta was observed in 6% (5/85) pregnancies in the study group, which is significantly increased in comparison to the overall population ($t = 5.05$, $p < 0.0001$).

Intrauterine fetal death was observed in all five pregnancies with abruptio placenta, in addition to the other fetuses with the fetal membrane anomalies noted in Table 6, with the exception of one with amniotic band complex and one with premature membrane rupture.

Fifteen percent of pregnancies in the study group resulted in live births of less than 37 weeks gestation (Table 7). The study group had a significantly higher preterm delivery rate in comparison to the general population incidence ($t = 5.03$, $p < 0.0001$). The percentage of preterm males did not differ significantly from the percentage of preterm females.

Twenty-two percent of the pregnancies in the study group were of LBW. The study group had a significantly higher number of LBW infants than observed in the general population ($t = 4.38$, $p < 0.0001$).

Nineteen percent (22/118) of live born infants in the study group were small for gestational age (SGA), compared with 10% from the general population. The study group contained a significantly higher number of SGA infants ($t = 3.26$, $p = 0.0006$). Sixty-one percent (72/118) of infant's weights were less than the 50th percentile for gestational age, which was significantly greater ($t = 2.39$, $p = 0.0084$) than expected. The percentage of infants large for gestational age (14%) in the study group was not significant ($t = 1.45$, $p = 0.0735$).

DISCUSSION

Initially, MSAFP screening was implemented as a test to detect pregnancies in the general population at high risk for spina bifida. In the last two decades, there have been numerous studies documenting the association between elevated MSAFP values and adverse pregnancy outcome. The current protocol for pregnancies with elevated MSAFP is to perform diagnostic ultrasound examination, which reveals an explanation for the elevation in about half of the cases [14]. When no apparent reason for the elevation can be found, amniocentesis is recommended to rule out open spina bifida. The key

TABLE 7. Live Births of Preterm or LBW Infants In Women With Unexplained MSAFP Elevations

Preterm/LBW	# Males	# Females	Total	Percent
<37 Weeks gestation	10/65	8/53	18/120	15*
<2.5 Kg	15/65	11/53	26/120	22*

* $p < 0.0001$.

finding of this study was that 40% of amniocenteses performed could have been avoided by using ultrasound reduced-risk estimates; moreover, no open spinal defects or ventral wall defects would have gone undetected. While the total number of affected pregnancies within the study group was fairly small, these data represent a three year study at a genetic center in an area of high neural tube defect incidence.

Birth information was available in 86.3% (139/161) of pregnancies. Pregnancy outcomes were classified as live births, therapeutic terminations (open spina bifida prenatally detected and electively terminated), and fetal loss (miscarriage and stillbirths). Eighty-six percent (120/139) of pregnancies in the study group resulted in live births, 12% (16/139) resulted in fetal loss, and 2% (3/139) resulted in therapeutic terminations. This demonstrates a significantly increased rate of fetal loss in comparison to the 3.5% rate of fetal loss following amniocentesis in the general population [13]. The increased incidence of miscarriages and stillbirths observed in women with unexplained MSAFP elevations supports similar reports in the literature. Bennett [15] reported a fetal loss rate of 16% after second trimester amniocentesis in women with unexplained MSAFP elevations.

Major congenital malformations were observed in 4.3% (5/117) of live births to non-insulin dependent (non-IDDM) women in the study group compared with 1.2% of live births to non-IDDM women in the general population [16]. This represents a significantly higher number of women in the study group who had infants with major malformations. Thirteen percent (2/16) of fetuses lost in the study group due to miscarriage and stillbirth had major malformations. By contrast, Mikamo [17] studied 64 pregnancy losses after 17 weeks gestation and found a 3% malformation rate. Thus, the study group exhibited a significantly increased rate of malformations in fetal losses. In addition, three cases of open spina bifida were detected, further increasing the malformation rate seen in the study group. The high number of major malformations observed in pregnancy outcomes in the study group is not surprising since an increased number of malformed infants have been reported previously in women with elevated MSAFP values [18, 19].

Condition of fetal membranes was reported in about half (53%) of the pregnancies in the study group. Placenta previa was documented in 1.2% (1/85) of pregnancies in the study group, while observed in approximately 1 in 250 pregnancies in the general population [20]. Since the number of pregnancies with reports of fetal membrane status was small (85), no definite conclusion can be drawn concerning significance of placenta previa in the study group. Abruptio placenta was observed in 6% (5/85) of pregnancies in the study group and only 0.83% (1/120) in the population overall [20]. It appears that women with increased MSAFP values have a much greater risk of abruptio placenta than individuals in the general population. This is of

importance since the overall perinatal mortality attributable to abruptio placentae is almost four per thousand, representing 15% of all perinatal deaths [20].

Twenty-two percent of pregnancies in the study group resulted in LBW infants, while only 10% with normal MSAFP values, which were subject to amniocentesis, resulted in infants weighing <2.5 kg [21]. Therefore, the study group had a significantly higher number of LBW infants. Wald et al [5], reported that 15% of infants born to women with MSAFP elevations weighed <2.5 kg. These findings suggest that high MSAFP levels in early pregnancy are associated with conditions leading to LBW. Since LBW is the single most important determinant of perinatal survival, infants born to mothers with elevated MSAFP values are at increased risk for perinatal mortality, which is 142/1000 in the United States for LBW infants [22].

LBW may result from a preterm delivery, or intrauterine growth retardation (IUGR). Fifteen percent of pregnancies in the study group resulted in preterm births (<37 weeks gestation). By comparison, 5% of women with normal MSAFP values who had an amniocentesis had live births of less than 37 weeks gestation [21]. The study group had a significantly higher preterm delivery rate. Previous studies have also shown a significant increase in the number of preterm infants in women with elevated MSAFP values. Studies in England and Scotland found 24% and 26% of infants born to women with MSAFP elevations were preterm [21].

Sixty-one percent of the study group had live births weighing less than the 50th percentile for gestational age, and 19% had infants who were small for gestational age (<10th percentile). The study group had a significant number of infants who were small for gestational age, which is in agreement with other studies of women with elevated MSAFP values. Hamilton et al [21] previously reported a 28% rate of IUGR among women with elevated MSAFP values who had amniocentesis.

Thus, it appears that women with unexplained MSAFP elevations are at increased risk of having both preterm and small for gestational age infants. Pregnancies in women with unexplained MSAFP values should be considered to be high risk since LBW is associated with increased likelihood of newborn death and long-term mental and physical disability.

The percentage of anomalies documented in "good" quality ultrasound scans was about the same as that noted on all scans. Although one might interpret this to mean that the quality of the ultrasound examination makes little difference in the ability to detect anomalies, this more likely reflects caution on the part of the ultrasonographer when anomalies are present. In addition, some fetal anomalies may cause the fetus to assume an abnormal position, making it difficult or impossible for the ultrasonographer to complete his ultrasound exam. Other fetal anomalies may be accompanied by oligohy-

dramnios, reducing the contrast the amniotic fluid normally provides, and decreasing ultrasound scan quality.

Most screening programs recommend amniocentesis as the current protocol for all women with unexplained MSAFP elevations. Midtrimester amniocentesis has been reported to increase one's risk of miscarriage from 0.3% to 1.0% above the general population. Moreover, the risk of fetal loss in the case of unexplained MSAFP elevation may be as great as 11% (Table 7). Women with elevated MSAFP values should be informed of the additional risk of fetal loss from amniocentesis over their current risk of fetal loss [23], and weigh this against the likelihood of detecting a neural tube defect in their pregnancy. The decision to proceed with the amniocentesis requires fully informed consent.

The purpose of this study was to determine if ultrasound-revised neural tube defect risks may prove to be a valuable tool for avoiding unnecessary amniocenteses. Open spina bifida risks were calculated for women with elevated MSAFP values unexplained by ultrasound examination. The woman's risk, based on her most recent MSAFP test, was reduced by 80% if she had a "good" quality ultrasound examination revealing no anomalies. Diagnostic ultrasound has been shown to have an estimated detection sensitivity of 100% for anencephaly and 80% for open spinal defects [24]. Given the recent improvements in the technology of ultrasonographic signs associated with open spina bifida, detection sensitivity now may be even higher.

The key finding in the study revealed that using ultrasound-revised risks for open spina bifida and an amniocentesis cutoff of 1 in 200, 40% of the amniocenteses in the study group could have been avoided without missing a single open spinal defect or ventral wall defect. While the number of cases of spina bifida was fairly small, the numbers reflect three years experience in MSAFP screening of 14,692 patients in an area of the U.S. with a high incidence of neural tube defects. Although "good" quality diagnostic ultrasound did not identify four pregnancies in which further testing revealed elevated amniotic fluid AFP values (two with positive acetylcholinesterase patterns) without neural tube defects, an amniocentesis would have been indicated in each case under the alternate protocol based on the calculated risk of open spina bifida. The revised risk remained greater than 1/200 for open spina bifida in women whose initial MSAFP value was approximately 3.0 multiples of the median or greater, depending on race and IDDM status.

The two chromosomal abnormalities detected by amniocentesis that would have gone undetected using the altered protocol included a 47,XYY, and 46,XY,inv(6)(p12q23) (a balanced de novo inversion). Both pregnancies were electively continued and resulted in live births without apparent physical malformations. The discovery of these chromosomal anomalies among those with unexplained MSAFP elevations most likely was coincidental.

Drugan et al [8] reported that an experienced ultrasonographer missed 25%

of the malformations in high-risk pregnancies; therefore, they concluded that a normal ultrasound does not obviate the need for amniocentesis in patients with elevated MSAFP values. The results of the present study support this finding as "good" quality diagnostic ultrasound failed to identify one pregnancy with multiple malformations secondary to amniotic band complex (Table 5). However, when one uses a "good" quality ultrasound examination to revise the risk of a pregnancy being affected with a spinal defect, many amniocenteses could be avoided.

Adams et al [23] suggested categorizing women into three groups of risk: high (risk more than 1:100), intermediate (risk between 1:100 and 1:400), and low (risk less than 1:400). The women in the low-risk group would be informed that amniocentesis is not necessary. The high-risk group would be counseled to have amniocentesis, and the intermediate group would be counseled that either action would be acceptable.

This system implies that a patient only is involved in the decision to have an amniocentesis if her risk should fall between 1/100 and 1/400. All patients should be given the autonomy to make their own decision regarding amniocentesis by considering their personal values and weighing the risk estimates for open spina bifida and amniocentesis. Genetic counselors and high-risk obstetricians often meet the patient for the first time when this difficult decision must be made. Therefore, they rarely can fully appreciate all of the patient's internal values that may play an integral role in the decision-making process. If non-directive yet informative counseling is to occur, the patient needs to be provided with the most accurate risk estimates for a neural tube defect and for the amniocentesis procedure, as this will facilitate her decision-making. All women with unexplained elevated MSAFP values should be given the opportunity to choose or refuse amniocentesis regardless of their revised-risk estimate.

A woman's open spina bifida risk could be used to determine if there is an "indication" for amniocentesis, however. An indication for an amniocentesis may be defined as a risk for open spina bifida that exceeds 1 in 200. This may serve as a guideline for persons who have difficulty interpreting quantitative risk estimates and desire more direction when considering their open spina bifida risk. Whether or not there is an "indication" for amniocentesis, a woman with an unexplained MSAFP elevation should be offered diagnostic testing as an option.

The altered protocol for revising a woman's risk for open spina bifida based on diagnostic ultrasound should be considered only when a patient's race, insulin status, family history of neural tube defect(s), geographic residence, and MSAFP value are known to give the woman an initial risk estimate for a neural tube defect. Also, the patient should receive genetic counseling describing neural tube defects, their clinical variability, the benefits and limitations of ultrasonography and amniocentesis, and the risk of the amniocentesis proce-

ture. The risk based on the woman's most recent MSAFP result should be discussed in addition to a revised risk for open spina bifida should she have a "good" quality ultrasound with no detectable anomalies. This may enable the patient to consider whether she desires the amniocentesis based on her initial risk estimate and her ultrasound revised-risk estimate. Risks should only be revised following a "good" quality ultrasound performed by an experienced ultrasonographer, with no detectable anomalies.

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Clinical and Laboratory Experience With Early Amniocentesis

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INTRODUCTION

Amniocentesis at 12 to 14 weeks gestation is a technique that is becoming increasingly utilized as an alternative to routine amniocentesis or chorion villus sampling (CVS) for fetal chromosome analysis. Direct ultrasound monitoring of needle insertion has allowed for greater safety and success in sampling smaller amniotic fluid volumes, and in situ culture methodology has allowed for use of smaller amniotic fluid samples and lower cell concentrations. The appeal of early amniocentesis and of CVS is that results are available earlier in pregnancy.

A project was undertaken to summarize and evaluate clinical and laboratory experience with early amniocentesis for cytogenetic analysis at the Prenatal Diagnostic Center in Lexington, Massachusetts.

From July 1985 through April 1989, 348 early amniocentesis samples were analyzed. One hundred forty-seven of these samples were from patients who had early amniocentesis at the Prenatal Diagnostic Center (PDC). The remainder were laboratory samples accepted from referring obstetricians. Presently, early amniocentesis patients make up 4.4% of the PDC clinical case load. Amniotic fluids obtained at 12 to 14 weeks gestation constitute 6.6% of the amniotic fluid samples processed in the laboratory.

A comparison was made to cases in which routine amniocentesis was performed at the PDC or by referring obstetricians in the Boston area during the same time period. An attempt was made to age-match the controls with PDC early amniocentesis patients. The average age of the PDC early amniocentesis patients was 37.7 years, compared to 38.0 for PDC routine amniocentesis patients. The average age of patients in the referred early amniocentesis group was 36.6 years. The average age of the physician-matched control group was 36.5 years.

A major difference was noted in the gestational age at which early amniocentesis at the PDC was performed when compared to the outside referral group. Forty-six percent of the PDC early amniocenteses were performed at 12 weeks gestation, 38% at 13 weeks and 14% at 14 weeks. In comparison,

12% of the referred early amniocentesis group were tested at 12 weeks, 18% at 13 weeks and 70% at 14 weeks.

Guidelines have been offered by the PDC to referring obstetricians and to patients in terms of who may wish to consider early amniocentesis. Maternal age ≥ 40 , the diagnosis of a chromosome abnormality either in a previous child or in a previous pregnancy, or the presence of a parental translocation are suggested as indications for early amniocentesis. CVS is also offered as an option to patients requesting information about early prenatal diagnosis.

Although the vast majority who had early amniocentesis were advanced maternal age (AMA) patients, 18.4% of the early amniocenteses performed at the PDC were for the indication of a previous chromosome abnormality, compared to 5% of patients whose samples were referred. Additionally, 3.4% of the PDC patients had parental translocation as an indication, compared to 0.5% of the referred early amniocentesis patients.

None of the patients who had early amniocentesis at the PDC were less than 35 years old. In contrast, 12% of the referred early amniocentesis patients were younger than age 35. Fifty percent of the patients having early amniocentesis for AMA at the PDC were 40 years or older (average 39.2 years); 23% of referred early amniocentesis patients with AMA as an indication were ≥ 40 years old (average 37.3 years).

RESULTS

The success rate for early amniocentesis performed at the PDC has been 97.3%, with 4 of 149 failed taps. Two of these failures were secondary to uterine cramping and one resulted from tenting of the membranes. Of these four patients, two were still tested in the 12 to 14 week time frame, and two were tested at ≥ 15 weeks. Early amniocentesis at the PDC is deferred if the gestational age is earlier than 12 weeks, if the maternal bowel is overriding the uterus, if cramping is noticed before the procedure is undertaken or if there is no placenta-free needle path. One procedure was deferred due to the presence of a large subchorionic hematoma which was secondary to a failed CVS attempt, another due to the presence of a large fibroid. Most early amniocentesis patients are scheduled at the PDC during their 12th or 13th week, which allows time for any deferred procedures to be performed at 13 or 14 weeks.

In the PDC early amniocentesis group, two cases required two needle insertions to obtain the amniotic fluid sample. In the PDC routine amniocentesis group, there were also two cases in which two needle insertions were necessary. No more than two needle insertions were made in any case.

The amount of amniotic fluid withdrawn has been limited in early amniocentesis due to the smaller total volume of fluid. The guideline that has evolved is

to withdraw 1 ml per week of gestation. At the PDC however, there is a tendency to remove even less fluid, resulting in an average volume for 12, 13 and 14 weeks of 9.4, 10.1 and 13 ml, respectively. The average volume was 10.1 ml. The referred early amniocentesis samples averaged 16.6 ml (9.6 at 12, 15.9 at 13, 18.1 at 14).

Because of the smaller amniotic fluid volumes obtained in early amniocentesis, fewer coverslips were set up per case for both referred early and PDC early cases. In 19% of the referred early cases and in 65% of the PDC early cases, only two or three coverslips were set up per case, in comparison to 0.54% for referred routine cases and 2.2% for PDC routine cases.

Average time to harvest of first coverslip for routine cases, both referred and PDC, was 7.3 days. For the referred early samples, the average time to first harvest was 7.8 days. For the PDC early samples, the average time to first harvest was 8.4 days. The increased time to first harvest for PDC early samples was attributed to the fact that early amniocentesis at the PDC is performed at earlier gestational ages; less fluid is taken and cell concentrations are lower.

The average completion time for a referred routine case at the PDC in 1989 was 12.6 days; the average completion time for PDC routine cases was 12.3 days. Referred early cases were completed in an average of 13.8 days and PDC early cases were completed in an average of 15.1 days.

Of the total of 348 early amniocentesis fluids analyzed in the laboratory, seven resulted in repeat procedures because of cell culture failure or an incomplete cytogenetics study. There were no cases of unexplained mosaicism or suspicion of maternal cell contamination which would have necessitated further testing. In 5 of the 7 cases, fewer than 15 counts from 7 colonies were obtained, but preliminary results were available to patients. Of the 2 cases in which no cytogenetic information was obtained, one was an 11-week sample, and one was grossly bloody. If the two 11-week samples, the one brown sample and the one bloody sample are removed from the group of seven retested cases, the repeat amniocentesis rate for patients with a clear amniotic fluid sample obtained at 12 to 14 weeks is 0.86%.

Follow-up information was obtained on 89% of the 182 babies who had been born in the referred early group, 96% of the 131 babies who had been born in the PDC early group, 89% of the 167 babies in the referred routine group and 94% of the 119 babies born in the PDC routine group. The referred and PDC cases were combined into early and routine groups to assess obstetric complications and pregnancy outcome.

The rate of obstetric complications within four weeks of the procedure in the early amniocentesis group was higher than the rate in the routine group: 0.3% of early amniocentesis patients reported cramping vs 0.8% in the routine group; 2.1% reported fluid leakage vs 0.4% in the routine group; and 1%

reported vaginal bleeding in comparison to 0% in the routine group. Of the ten cases in which cramping, fluid leakage, or vaginal bleeding was reported in the early group, there were two induced abortions, but no spontaneous pregnancy losses. Therefore, although the rate of obstetric complications postprocedure may be higher with early amniocentesis, these complications seem likely to resolve.

The pregnancy loss rate in the early ($N = 348$) and routine ($N = 324$) amniocentesis groups was assessed. There were 9 induced abortions (2.6%) in the early group and 3 (0.9%) in the routine group. The spontaneous loss rates at <20 weeks, 20 to 28 weeks, and >28 weeks were 2.3%, 0.8% and 0.3% for the early group, and 0.3%, 0.3% and 0% for the routine group.

A much larger series needs to be examined and statistically analyzed before conclusions can be drawn in regard to the precise level of risk posed to pregnancy by early amniocentesis. But comparisons of loss rates at various gestational ages to loss rates of both the CVS and routine amniocentesis patients analyzed in the U.S. and Canadian CVS studies indicate that early amniocentesis can be very reasonably considered as one of the options currently available for prenatal diagnosis. (See Tables 1 and 2.)

Type of delivery, birth weight, and APGAR scores were also compared between early and routine groups. Thirty-two percent of the early amniocentesis group had cesarean section compared to 30% of the routine group. The average birth weight for the babies in the early amniocentesis group was 3470 gm in comparison to 3442 gm for the routine amniocentesis group. The average five minute APGAR score for the early amniocentesis group was 8.97, and the average for the routine cases was 9.05.

The rate of birth defects in the early and routine groups was assessed. In the early amniocentesis group, one case of clubfoot, two congenital heart defects, one case of dwarfism, and one knee deformity were reported, for a rate of 1.7%. In the routine group, one congenital heart defect and one congenital hip dislocation were reported, for a rate of 0.8%. In 2.3% of the early group and in 0.9% of the routine group, a fetal abnormality had been detected prenatally. The total rate of birth defects in each group is within the established background risk in the general population.

TABLE 1. Spontaneous Loss Rates

	U.S. CVS Study			PDC Study	
	CVS	Amnio		Early	Routine
After CVS, before second-trimester evaluation	2.2	?	12-15 wks	1.1	—
After second-trimester evaluation, before 28 weeks	1.2	1.0	16-28 wks	2.0	0.6
After 28 weeks	0.4	0.6	After 28 wks	0.3	0

TABLE 2. Spontaneous Loss Rates

	Canadian CVS Study		PDC Study	
	CVS	Amnio	Early	Routine
12-15 weeks	1.7	1.4	1.1	—
16-24 weeks	1.8	1.3	1.4	0.6
After 28 weeks	0.5	0.1	0.3	0

Data were also gathered in regard to neonatal complications in the two groups. In the early amniocentesis cases, one case of Erb palsy, three of infection, two of jaundice, one of seizures, and one of thrombocytopenia were reported, for a rate of 2.8%. In the routine group, one pneumothorax, one infection, one meconium staining, one pulmonary hypoplasia and one case of respiratory distress syndrome (RDS) were reported, for a rate of 1.9%. It is noteworthy that none of the cases of fetal pulmonary dysfunction occurred in early amniocentesis patients.

A critical point in examining the data on early amniocentesis is that the very high degree of accuracy of the cytogenetic testing associated with routine amniocentesis is retained. In the 288 cases in the early amniocentesis group for which follow-up information has been obtained, there were no discrepancies between cytogenetic results and phenotype. No cases of maternal cell contamination were reported.

CONCLUSIONS

For patients who prefer cytogenetic results earlier in pregnancy, amniocentesis at 12 to 14 weeks is an alternative in which safety, success and accuracy is being demonstrated. From the standpoint of health care delivery, the processing of 12-14 week amniotic fluid samples can be integrated into a cytogenetics laboratory with no significant changes in equipment, technique or procedures if an in situ methodology is already operative. Because of these factors, early amniocentesis is being offered and selected as a means for prenatal diagnosis with increasing frequency. New techniques such as the polymerase chain reaction could make early amniocentesis applicable for prenatal testing for disorders other than chromosome abnormalities and utilization may dramatically increase.

As advances in reproductive technology take place, couples are being offered more choices for prenatal screening and diagnostic testing. Their decisions will continue to depend on their perception of risk for an affected child, the willingness to accept a level of risk to the pregnancy to obtain diagnostic information and the personal context within which the risks and benefits of various procedures are weighed.

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Chorionic Villus Sampling Mosaicism: Counseling Issues

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INTRODUCTION

Chorionic villus sampling (CVS) was first used successfully by the Chinese in the early 1970s. In 1981–82, modern methods for karyotyping CVS specimens were devised. With the growing availability of improved real-time ultrasound equipment, interest in first trimester diagnosis became widespread. Developments in CVS technique have continued. Three types of ultrasound-guided CVS procedures are currently available: 1) transcervical; 2) transabdominal; and 3) transvaginal. Analysis of chorionic villi can provide information regarding karyotype, DNA composition, and enzymatic or other biochemical parameters of the fetus. Results can be obtained in the first trimester with reliability similar to that of amniocentesis.

Questions regarding appropriate genetic counseling in cases of CVS mosaicism have been raised. Mosaicism for the purpose of this report is defined as the identification of at least two abnormal cells with the same cytogenetic abnormality in the presence of normal cells in trophoblasts or cultured villi. Mixtures of normal male/normal female cells are excluded, since this is considered to be due to maternal cell contamination. To provide appropriate counseling after CVS mosaic results have been identified, three factors need to be considered: the incidence of mosaicism in CVS, the interpretation of mosaic results, and the significance of the particular mosaicism.

INCIDENCE

In our experience at the Genetics and IVF Institute the incidence of CVS mosaicism is approximately 1.1%. Fifty-three mosaics occurred in 4,737 consecutive samplings. This percentage is similar to that reported by the few other centers where over one thousand samplings have been performed.

INTERPRETATION

Interpretation of results requires understanding the possible types of mosaicism including: 1) true fetal mosaicism; 2) confined placental mosaicism; or 3) tissue culture artifact.

True fetal mosaicism occurs when a second cell line arises early in embryonic development and within the precursor cells of the fetus itself. Two types of cells would therefore be present in the fetus and phenotypic expression of that particular mosaicism could be expected.

Confined placental mosaicism occurs when a second cell line arises in placental precursor cells but not in fetal precursor cells. Two types of cells would then be present in the placenta, but not in the fetus. The fetus would then be expected to have one of the cell lines seen in placental tissue, but not both.

Tissue culture artifact occurs when a second cell line arises in tissue culture. In this instance, no evidence of the second cell line would be anticipated in placental tissue or in the fetus.

Determining the possible etiologies of mosaicism is crucial for accurate interpretation of results. Factors which influence this assessment include: 1) the number of abnormal cells and whether they occur in different cultures and in different cell types; 2) the likelihood of viability of the fetus at the current gestational age, assuming the mosaicism represents the true fetal chromosome constitution; 3) the incidence of the full or mosaic chromosome abnormality in the liveborn population.

If the *in situ* method of culture analysis is used, the finding of two or more abnormal cells in one culture with the remaining cells analyzed being normal is likely to represent tissue culture artifact. If abnormal cells are found in different cultures, this is more likely to represent confined placental mosaicism or true fetal mosaicism.

Mosaicism in a viable pregnancy, which is of a type not generally consistent with viability at that gestational age, is likely to represent a tissue culture artifact or confined placental mosaicism. Low-level mosaicism in the fetus cannot be ruled out, however.

Mosaicism is more likely to represent true fetal mosaicism if it is of a type having a relatively high incidence in the liveborn population, eg, Down syndrome mosaicism or sex chromosome mosaicism.

Amniocentesis is indicated to confirm or rule out fetal mosaicism when true mosaicism or confined placental mosaicism is suspected. Fetal blood sampling may also be appropriate on rare occasions. A list of our own experience with CVS mosaicism and follow-up amniocentesis of blood karyotype results is provided in Table 1. Mosaic tetraploidy is an exceptional example in that amniocentesis does not reliably confirm the presence of tetraploidy. Tetraploidy commonly occurs in amniotic fluid as a culture artifact (Milunsky, 1986). A false-positive confirmation of tetraploidy could occur. Fetal blood sampling may deserve careful consideration in these cases. It must be remembered, however, that no prenatal procedure can be 100% accurate in excluding mosaicism.

TABLE 1.

CVS Results	Amnio Results	Blood
Mos46,XY/47,XY,+2	46,XY	(Pending)
Mos46,XY/47,XY,+2	Declined	
Mos46,XX/47,XX,+3	46,XY	
Mos46,XX/47,XY,+3	46,XY	
Mos46,XX/47,XX,+7	Declined	
Mos46,XX/47,XX,+7	46,XX	
Mos46,XX/46,XY/47,XY,+7	46,XY	46,XY
Mos46,XY/47,XY,+8	46,XY	
Mos46,XY/47,XY,+9	46,XY	
Mos46,XY/47,XY,+10	46,XY	
Mos46,XY/47,XY,+10	46,XY	46,XY
Mos46,XX/47,XX,+11	46,XX	
Mos46,XY/47,XY,+12	46,XY	
Mos46,XY/47,XY,+12	46,XY	
Mos46,XY/47,XY,+12	46,XY	
Mos46,XY/47,XY,+13	46,XY	
Mos46,XX/47,XX,+13	46,XX	
Mos46,XY/48,XXY,+18	46,XY	
Mos46,XX/47,XX,+18	46,XX	
Mos45,X/46,XY	46,XY	
Mos45,X/46,XY	46,XY	
Mos45,X/46,XX	Pregnancy interrupted	Fetal sex
Mos45,X/46,XY	46,XY	
Mos46,XY/47,XXY	Mos46,XY/47,XXY	Mos46,XY/47,XXY terminated
Mos45,X/46,XY	46,XY	
Mos46,XX/92,XXXX	46,XX	
Mos45,X/46,XX	46,XX	
Mos46,XX/92,XXXX	46,XX	Mos46,XX/92,XXXX
Mos46,XY/92,XXYY	46,XY	(Pending)
Mos46,XY/46,XY,-13,+t(13q13q)	46,XY	
Mos46,XX/46,XX,-13,+t(13q13q)	46,XX	
Mos46,XY/46,XY,t(1;4)	46,XY	
Mos46,XX/46,XX,t(5;15)	Spontaneous abortion	
Mos45,XX,t(13q14q)/46,XX,-14,+t(13q14q)	45,XX,t(13q14q)	(Pending)
Mos46,XY/46,XY,r(1)	46,XY	
Mos46,XX/46,XX,1q-	46,XX	
Mos46,XY/46,XY,dup(1)(q32)	Declined	
Mos46,XX/46,XX,3q-	46,XX	(Pending)
Mos46,XX/46,XX,4p-	46,XX	
Mos46,XX/46,XX,6p+	46,XX	
Mos46,XX/46,XX,6p+	46,XX	

TABLE 1 (contd).

CVS Results	Amnio Results	Blood
Mos46,XX/47,XY,+i(18q)	46,XX	
Mos46,XX/46,XX,19q-	46,XX	
Mos45,XX,-21/46, XX/46,XX,21q+	46,XX	46,XX Neonatal death (gastroschisis)
Mos46,XX/47,XX,+22q-	47,XX,+22q-	
Mos46,XY/46,X,del(Y)	?45,X/46,X,?del(Y) (q11.23)/46,X,?psu dic(Y)t(Y;Y)(q12; ?q12)/ 46,X,psu dic(Y)t(Y;Y) (q121?q12),+f	Terminated
Mos46,XY/46,XY,+f	46,XY	
Mos46,XY/46,XY,+f	46,XY	
Mos46,XX/46,XY/46, XY,+f	46,XY	
Mos46,XX/46,XX,+f	46,XX	
Mos46,X,+mar/46, XY/47,XXY	Declined	46,X,+mar/46, XY/47,XXY
Mos45,X,+f/46, XY/47,XXY	46,XY	

SIGNIFICANCE

The significance of confined placental mosaicism has not yet been determined. Recent studies have demonstrated that mosaicism detected at CVS can often be confirmed in placental tissue after delivery of healthy infants. Ongoing studies will determine the significance of abnormal cell lines in placental tissue. Most infants have been delivered at full-term following CVS mosaic diagnosis. Literature reports of phenotypic expression of mosaicism may be available. When possible fetal mosaicism is diagnosed, the literature should be reviewed, and, in some cases, discussion with professional peers should be considered prior to counseling.

COUNSELING

It is desirable to discuss the possibility of mosaicism prior to any CVS procedure. Counseling of a couple following a diagnosis of CVS mosaicism should include an explanation of the presence and likely etiology of the particular mosaicism. The risks and benefits of follow-up procedures such as amniocentesis need to be addressed. Since true mosaicism is rare, couples are most often reassured by a counseling session. In our experience with 4,737 chorionic villus samplings through March 1988, the incidence of true fetal

mosaicism was 0.06%. Three of 53 CVS mosaics were confirmed postnatally or after termination of the pregnancy (5.7%).

CONCLUSION

CVS mosaicism should not be viewed as a prohibitive complication of first trimester diagnosis. Results can be prospectively interpreted, appropriate genetic counseling provided and additional fetal testing made available.

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Cytogenetic Discrepancies in CVS: Genetic Counseling Issues and Dilemmas

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Chorionic villus sampling (CVS) was first performed in the United States in 1983. CVS was developed as a first trimester alternative to amniocentesis which produces results of chromosomal, biochemical and DNA analysis more rapidly than amniocentesis since villi cell growth is quicker. Chromosomal analysis from direct preparations of actively dividing trophoblasts may be completed in one to five days. The ability to perform CVS in the first trimester of pregnancy and the decreased waiting time for results made CVS an attractive prenatal diagnosis choice for many women. Short-term culture of chorionic villi is preferred in many laboratories because chromosome resolution is clearer and technically simpler. Tissue culture results usually take from one to three weeks. There is now evidence that tissue culture may more accurately reflect the chromosomal makeup of the fetus than the direct preparations. The experience of the Section of Reproductive and Medical Genetics at Illinois Masonic Medical Center in over 4,000 CVS cases, as well as the data derived from the NICHD National Collaborative CVS and Amniocentesis Study, in which we participated, indicate that in a small but significant proportion of cases, discrepancies arise between the two CVS cultures. Although it was originally thought that all placental tissue derived from cells originating with the fertilized egg, and therefore, accurately represented the chromosomal makeup of the fetus, issues regarding mosaicism, pseudomosaicism, artifacts and discrepancies have arisen. In many cases, further testing by amniocentesis or PUBS is necessary to provide an accurate assessment of the fetus. These situations present a number of unique genetic counseling issues and dilemmas, including increased anxiety, anger at the limited information available, difficulties in presenting embryologic information, and issues surrounding termination of pregnancy and privacy.

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The Observation and Karyotypic Implications of Cystic Hygroma in the First Trimester

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INTRODUCTION

The emerging use of chorionic villus sampling (CVS) as a method for first trimester prenatal diagnosis has greatly increased the number of first trimester ultrasound examinations. This increased experience, coupled with improved image resolution, has resulted in the earlier discovery of fetal structural abnormalities. Cystic hygroma or lymphangioma resulting from functional failure of the cervical lymphatic flow into the venous system, is one type of anomaly being observed. When identified in the second trimester there is a 40–70% probability of a karyotypic abnormality and over a 90% chance of fetal death or phenotypic abnormality. We identified ten cases of fetuses with cystic hygromas during the first trimester. Karyotypes were performed and the pregnancy outcomes were determined.

METHODOLOGY

During the period from September 1984 to September 1989, approximately 7,000 CVS procedures were performed at our institution. Women participating in this program were asked to have a pre-procedural ultrasound examination to determine viability and gestational age. These scans were performed between 6–10 weeks gestation at a variety of institutions, utilizing sonographers with a wide range of experience. Transabdominal ultrasound examination was again performed immediately prior to the CVS procedure at our institution by experienced sonographers between 9–12 weeks gestation. Karyotyping had already been requested by all women in the program and every effort was made to offer rapid results in every case in which a fetal anomaly was detected by ultrasound. A genetic counselor was involved in the management of every patient.

RESULTS

Ultrasound examination directly prior to the CVS procedure revealed ten cases of cystic hygroma of the neck, an incidence of 0.14%. Seven of these

cases originally presented for advanced maternal age, one for a known parental chromosomal translocation and two for routine scans. Mean gestational age at the time of diagnosis was 11.7 weeks (range 10.5–12.7 weeks). Prior scans performed at 6–7 weeks (3), 9 weeks (2), and 11–12 weeks (2) on the same fetuses failed to demonstrate the abnormality. CVS followed by rapid karyotype analysis was successful in all ten cases. The results revealed four cases of trisomy 21, one case of trisomy 13, two cases of 45,X, one case of 45,X/46,XY (in one sample from a twin pregnancy), one case with an unbalanced translocation (mother was a known balanced translocation carrier), and one case of a normal 46,XX karyotype (see Table 1). Of the nine women with chromosomally abnormal pregnancies, eight electively terminated and the ninth spontaneously aborted at 20 weeks. The chromosomally normal fetus was scanned again at 13 weeks, at which time the cystic hygroma was no longer visible. A liveborn female was delivered at 31 weeks gestation secondary to toxemia and fetal intrauterine growth retardation. The neonate had no cystic hygroma or nuchal thickening upon delivery and is doing well at two months of age.

DISCUSSION

Prenatal diagnosis of cystic hygroma in the second trimester is well documented [1]. Abramowicz et al [2] have reported an incidence of 0.16% with 60–70% being chromosomally abnormal. Of those with abnormal karyotypes, 40–80% show the Turner syndrome. Pregnancy outcomes in these pregnancies have been generally poor, with 93% of those electively continued resulting in spontaneous abortion, stillbirth or neonatal death. Of the survivors (all of whom were karyotypically normal) only 2–3% were phenotypically normal [2]. Cystic hygroma diagnosed after birth has a more benign prognosis and

TABLE 1. Present Series

Case	Indication for Scan	Weeks at Detection	Fetal Karyotype Result	Pregnancy Outcome
1	Mat: 45,XX+t(1;18)	11.1	46,XY+t(1;18)	TAB
2	MA-48	12.7	47,XX+21	TAB
3	Routine	12.0	45,X	TAB
4	MA-44	11.9	47,XX+21	TAB
5	MA-35	10.5	46,XX	Normal
6	MA-38*	11.8	45,X/46,XY	TAB/SAB
7	MA-38	11.1	47+13	TAB
8	Routine	12.0	47+21	SAB
9	MA-39	12.3	47+21	TAB
10	MA-35	11.8	45,X	TAB

*Twins

tends not to be associated with chromosomal abnormalities. Surgical repair is generally a definitive therapy [3].

In contrast, detection of cystic hygroma in the first trimester is strongly associated with karyotypic abnormalities. In this limited series, 9/10 of cases demonstrated chromosomal abnormalities, with only two of those representing Turner syndrome. This high incidence may be somewhat biased by our group of advanced gestational age patients. However, when diagnosed before or during the 12th week, rapid karyotyping should be offered to these patients. Some hygromas with normal karyotypes may resolve as the pregnancy progresses. Further work is required to elucidate the ultrasound differentiation of hygromas that are benign and will resolve.

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Abortion Update Address to National Society of Genetic Counselors Annual Meeting, November 11, 1989, Baltimore, Maryland

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Over four years ago, when the *Webster* case wasn't even a gleam in our eyes, if you'll pardon the expression, I had the privilege of introducing the novelist John Irving at a gathering in Washington. It was just after the publication of *The Cider House Rules*, the story of a turn-of-the-century New England birthing center, adoption agency, and abortion clinic, all rolled into one. One of the two heroes of the novel was an obstetrician and an abortionist, a rather unusual combination in that time and place. And in one of his musings about his career choices, he summed them up rather nicely: "I deliver babies," he said, "and I also deliver mothers." I found his words poignant when I quoted them to their author in 1985, and I still do today.

But today, the rights of babies, and mothers, and I guess all the rest of us, are looking quite different. The rendering of this decision has marked a turning point, for better or worse—and I do believe it is both—in the law and the politics of reproductive rights; and it is my duty—and honor—to address this subject, both what has come before and what we should expect from the future.

It is hard to be involved in the abortion issue these days and not be feeling rather buoyant—that pro-choice majority we always talked about really is there and has become energized to an extent few would have imagined even six months ago. You are all familiar, I am sure, with the electoral and legislative victories, both state and—unheard of—federal! There have been and will be exceptions, but it is clear that Americans take the right of privacy seriously, whether the Supreme Court does or not. In a slightly different arena, I myself have witnessed first-hand the rising of the pro-choice groundswell. On October 14, we filed an *amicus* brief in the Supreme Court cases which was signed by 274 organizations—more than have ever signed an *amicus* brief on any issue in the history of the Supreme Court! The groups signing this brief ran the gamut of American political life and included some who have never been involved in this issue before—like the Southern Christian Leadership Conference. It also included 30 Nobel laureates, 497 law professors, and the National Society of Genetic Counselors, among many others.

Yes, we all have a lot to be happy about, but let's not kid ourselves: the *Constitutional* right to a safe and legal abortion has never seemed so precarious. The importance of *Roe v. Wade*, and its continued vitality, is that it recognized the right to abortion as a federally guaranteed, constitutionally protected right, thereby limiting the ambit of permissible state regulation. The effect of the *Webster* decision—though its precise meaning is unclear to virtually everyone who has read it—is that it casts doubt on the status of the abortion right as a *fundamental* right, thus giving the states more leeway to derogate from it.

And let there be no mistake about it: four of the nine Supreme Court Justices are ready to abandon the trimester system altogether. In this effort, they are being egged on by the so-called kinder and gentler Bush administration, first in the person of the Solicitor General of the United States, whose brief in the current Supreme Court cases goes beyond even the regressive jurisprudence urged by Charles Fried in the Reagan regime. And the President's recent vetoes of three abortion-friendly statutes makes it perfectly clear where he has positioned himself on this issue. I can only anticipate with horror the imminent prospect of three Supreme Court vacancies for him to fill.

As Justice Blackmun so aptly put it, the *Webster* decision issued an invitation to the states to enact ever more restrictive abortion regulations. It was an invitation they did not really need. Ever since *Roe*, and with increasing vigor, the anti-choice movement has been engaged in a concerted program on several fronts to *eliminate* the right to abortion. Aside from the obvious street campaign of harassment and intimidation, their legislative strategy is designed to employ more subtle means to the same end.

The statutes at issue in the Supreme Court cases are good examples of the categories they seem to favor. One is to peel off the most needy and least powerful constituencies—the poor, the young, minorities—and eviscerate their rights to exercise reproductive choices. Another is to so encumber the physicians and facilities providing abortions with onerous and useless regulations that they are literally forced out of business. Of special interest to counselors and health care professionals is the dangerous pattern of interposing the state between the doctor and the patient—prescribing who may counsel a woman seeking prenatal health care and about what.

Even in the midst of our euphoria about the serial victories against such state enactments, we must be mindful that there is no substitute for a *constitutional* right to abortion, which protects our fundamental rights from accidents of geography. Officials of Louisiana, for example, are now attempting to enforce an 1855 statute which penalizes doctors performing abortion to the tune of 10 years at hard labor. Pennsylvania is expected to enact an omnibus anti-abortion bill with something for everyone: spousal notification, parental notification, a 24-hour waiting period, and a ban on almost all

abortions after 24 weeks gestation. And just last week, the United States Court of Appeals for the Second Circuit ruled that family planning clinics receiving federal funds can be prohibited from providing abortion *counseling* to low income pregnant women.

Which brings me full circle—to the courts. The time has passed when we can depend upon the judiciary, particularly the Supreme Court, to be the guarantors of the right of reproductive choice. We must fight for this right in other arenas. This realization is especially painful for me, since I have spent most of the past seven years in monitoring the federal judicial selection process. In fact, just the other day I ran into a colleague in the judicial selection business who asked me what I was working on now. I answered, “the abortion issue,” to which she replied, “at least it’s a winning cause.” “But,” I said, “I’m working on it in the courts.” “Then you’re still fighting losing battles,” she rejoined. It seems to be a bad habit of mine.

I want to conclude by making a public confession. I was a law student, and a very political law student at that, when the decision in *Roe v. Wade* was announced in 1973. But I have absolutely no memory of where I was or how I felt when this momentous event in American legal history—not to mention women’s history—occurred. Absolutely no memory. But I do remember where I was when *Webster v. Reproductive Health Services* was read to a hushed Supreme Court chamber: I was in that hushed Supreme Court chamber. And I know where I’ll be when they fire the next salvo: in the same place. Because I want them looking out at a sea of women, women who have had babies and women who have had abortions and women who have had both; women whose children were planned and women who have made mistakes; women who have had problem-free pregnancies and women for whom bearing children was the riskiest of propositions. I want the courtroom filled with women who care enough about protecting their rights to stand in line at 6:00 AM the way some people suffer for Rolling Stones tickets—and I hope you’ll be there with me.

Prenatal Diagnosis Technology: Equal Access For All Women

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The rapid application of prenatal diagnostic technologies in human genetics has created difficult choices for families receiving services and for maternal and child health providers. Dr. John Fletcher has noted that "technology is not the source of ethics, but it creates alternatives that you never had before and you have to choose whether to act on one or more of the alternatives" [1].

The history of prenatal diagnosis began as recently as 1967, when the first report of a diagnosis of a chromosomal disorder from amniotic fluid appeared. In 1968, the first prenatal diagnosis of a metabolic disease was reported [2]. Prenatal diagnostic technologies have rapidly expanded in a short period of time. This paper will focus on a case report from the Hayward Genetics Center and discuss public policy issues associated with prenatal diagnosis.

CA was a 19-year-old G2P1 college student who asked her private obstetrician about the availability of prenatal diagnosis for sickle cell disease. She was subsequently referred to our center for genetic counseling. She and her husband were known to have sickle cell trait. She had a son from a previous union with sickle cell trait. CA was initially scheduled for counseling when she was 10 weeks pregnant. Our clinic was busy on that day and patients had to wait at least an hour to be seen. The patient opted to reschedule her appointment. She was seen at 13 weeks gestation, thereby eliminating the option of chorionic villus sampling.

We discussed amniocentesis, its risks, benefits and limitations. The methodology for prenatal diagnosis of sickle cell disease was explained. CA and her husband decided to undergo prenatal diagnosis for sickle cell disease.

We arranged for analysis at one of the university-based diagnostic centers, and obtained the necessary clinical information from the couple. We were told that results would be available in two weeks. CA contacted the center to arrange for billing her insurance company.

On March 16, 1988, we were notified by the diagnostic center that their cytogenetic laboratory had a mix-up and that the supernatant from the amniotic fluid had been discarded prior to alpha-fetoprotein determination. We were told that the cells were growing. On March 22, blood from the couple

was obtained and sent to the diagnostic center as requested for DNA analysis and electrophoresis.

On April 4, we were notified of the chromosome results. We were told that the sickle cell results were not available but would be ready within a week. On April 11, we were notified that the film was unclear and that a band analogous to HgbS was present, but that it could not be determined if other bands were also present. We were then told that we would be notified the following week of final results. On April 18, we received a phone report that "The fetus was predicted to be affected."

By this time seven weeks had elapsed, and CA was in her 23rd week of pregnancy. Termination of a pregnancy is not available beyond 20 weeks in Louisiana. Therefore, we requested that the diagnostic center assist us in arranging a termination if the couple chose this option.

When we met with the couple, CA was almost 24 weeks pregnant. We discussed the results and the implications. The option of terminating the pregnancy was raised by the couple. We explained that they would have to travel to the diagnostic center which was in another state. They chose to terminate and an appointment to see an obstetrician at the center was made for two days later. Meanwhile, the couple contacted CHAMPUS, their insurance company, to make sure that they would pay for the termination. They were told that the cost would be covered.

CA and her husband drove 5½ hours to the diagnostic center. The couple was seen in the obstetrician's office and initiation of dilatation was started. CA was reevaluated by the obstetrician the next day and instructed to report to "X" hospital the following day. At 7:30 a.m. the next day, the patient was admitted and an IV was started. Several hours after she was in her hospital room, the couple was informed that the hospital did not accept CHAMPUS insurance. They were told that they could go to a hospital 30 miles away that did accept CHAMPUS insurance and obtain a "non-availability" letter from that hospital stating that they could not do terminations. Once they obtained this letter they could be admitted to hospital "X." The obstetrician contacted the couple's obstetrician in Louisiana and suggested that the couple return home so that the procedure could be completed since this was a Sunday. The couple's obstetrician raised professional and medicolegal reservations about such an arrangement. However, he agreed, and the couple returned home and the procedure was completed.

In accordance with Louisiana regulation requiring a review of all fetuses of at least 23 weeks, the fetus was transferred to the coroner's office. Our records were also subpoenaed for review.

The development of genetic screening programs has greatly reduced human suffering and tragedy in some families and provided joy and happiness in

others through the birth of healthy children. The objective of many screening programs is precisely to enhance the quality of parental choices in reproduction. The provision of genetic information widens parental options, enriches the decision-making process and enlarges parents' freedom of choice [3]. Such prenatal diagnosis programs raise important questions:

- Who determines how the new technology is used?
- What are the proper ends of the technology?
- Does a new technology lead to new rights, for example, the right to be born healthy?
- Who has the opportunity to use the new technology? Is there equal access?
- Do new technologies pressure young families into feeling that they must produce a perfect child?
- Should scarce public dollars be targeted toward universal prenatal care or more sophisticated testing for fewer women?

These questions illustrate the many issues raised by prenatal screening programs. The President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research identified the main ethical principles as autonomy, beneficence, justice (including equity and fairness) and privacy (including confidentiality) [p. 41, ref. 2]. Recognizing that the issues are collectively too broad sweeping to adequately address, our focus will be limited to access to services.

The 1979 Report from the Hastings Center on Guidelines for the Ethical, Social and Legal Issues in Prenatal Diagnosis specifically addressed issues of access [4]. It stated that . . . "recognizing that the majority of women who undergo prenatal diagnosis belong to higher socioeconomic groups, the guidelines endorse wide dissemination of information and third party reimbursement for prenatal diagnosis." Further, in 1979, the report of the National Institute of Child Health and Human Development Consensus Conference on Prenatal Diagnosis [5] presented the following consideration: "equal access to such services for all must be assured. All services and options of care should be available to families . . . including prenatal care, considerations for care of the newborn, and when elected by the family, abortion services as well."

While there may appear to be some theoretic consensus on the issue of access, in reality, resources are not and perhaps will *not* be made available in the present health care system. Is this an acceptable situation?

As it relates to AFP screening (and can be applied to reproductive technologies as a whole), Leroy Walters [6] viewed the access issue as critical at the point of entry into a program and at the point where follow-up services may be required. In some cases, the initial cost of testing may deter a woman from participating. For women seeking care through public health clinics, the long waiting list for care may make them ineligible for screening by the time of

their first prenatal appointment. Late entry into prenatal care is an important problem related to prenatal testing. Specifically addressing AFP screening, Walters purports that justice would call for every pregnant woman who desires AFP screening to be offered access to screening and follow-up services without regard to her ability to pay or the comprehensiveness of her health insurance. "A woman who is told that her maternal serum AFP value is elevated, but who cannot afford genetic counseling, ultrasound or amniocentesis is probably worse off than a woman who has not been screened at all" [6].

The future of human genetics is certain to be more ethically complex than the present. Fletcher et al suggest that "facing complex issues with help from guidelines is better than facing them with the strength of convictions" [7]. We need a framework for public policy development. There are existing models, such as in the state of Maryland, for designing policy-making bodies that can aid in the difficult task of developing consensus on program direction. The President's Commission asserted that successful programs require concrete goals and specific procedural guidelines that are founded on sound ethical and public policy principles.

If the goal of any genetics program is to have a well-informed public capable of making knowledgeable decisions concerning reproduction and health, then programs have a responsibility to view the issues in a broad societal context. Here is the case of an intelligent, assertive and well-informed young woman who has what is desired for patients—a supportive and loving husband and family, and a caring and astute obstetrician and insurance. She was able to receive services at the front end. However, it was at the back end where reproductive technologic advances and their benefits failed—she was almost prevented from choosing the option of terminating her pregnancy.

The members of the International Society of Nurses in Genetics and the National Society of Genetic Counselors are unique in that they serve as liaisons to the medical community, families and the public. In that role, we are patient advocates and have a responsibility to assist in establishing and implementing policies that assure equal access for *all* women.

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Fetal Reduction and Selective Termination in Multifetal Pregnancy: Outcomes, Ethical and Counseling Issues

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INTRODUCTION

As reproductive technology has evolved, clinical situations have developed in which reduction of some embryos within a multifetal pregnancy has been demonstrated to enhance the probability of the birth of healthy neonates. The reduction of multifetal pregnancies resulting from ovulation induction techniques and the selective termination of a co-existing twin with a genetic abnormality have been described [1-14]. Previous reports, however, have been based on relatively small series of patients. Over the past two and one-half years, 46 cases of first and second trimester selective terminations of multifetal pregnancies have been performed at Jefferson Medical College. Procedures were performed for three indications and utilized a uniform technique. Patients were counseled extensively by a genetic counselor and a perinatologist prior to the procedure. The purpose of this paper is to describe the technique of selective termination, report the outcomes, and discuss clinical counseling and ethical issues.

PATIENTS AND METHODS

From September 1985 until May 1988, 46 women were referred to the Genetics and Fetal Medicine Unit at Thomas Jefferson University Hospital for selective termination in an attempt to improve the outcome of a multifetal pregnancy. Technical aspects of this procedure have been reported by us elsewhere [15]. Patients were classified into one of three groups based on their indication for the procedure:

Indication A:

To improve perinatal outcome and enhance the likelihood of the birth of a term newborn by reducing the number of fetuses in a multifetal pregnancy.

Indication B:

To allow the birth of a healthy liveborn without the birth of a co-existing fetus with a congenital abnormality.

Indication C:

To reduce a multiple pregnancy to a singleton pregnancy for social or personal indication.

TERMINATION PROCEDURE**Indications A and C**

Procedures for indications A and C were performed between nine and 13 weeks from the last menstrual period. Real-time ultrasound scanning was performed to identify fetal position and evaluate growth. If all fetuses had similar crown-rump lengths, the one in the most technically accessible position was chosen. The fetus overlying the cervix was excluded to avoid the theoretic risk of ascending infection.

A 22-gauge spinal needle was sonographically guided into the fetal pericardial region. Once the needle was in place, 0.2–0.4 cc increments of sterile KCl solution (2 meq/ml) were injected until cardiac activity ceased. From 0.2 cc to 1.8 cc of KCl were required. Once ultrasound visualization of the heart confirmed asystole for at least 60 seconds, the needle was readjusted into the amniotic sac and 10–15 cc of amniotic fluid were removed. If more than one fetus was to be terminated, subsequent fetuses were identified and a similar procedure repeated. As many as four fetuses were terminated at one session. Thirty minutes following the procedure, the fetal heart was rescanned and if cardiac activity was identified in a fetus previously injected with the cardiotoxic substance, the procedure was repeated the same day. No prophylactic antibiotics or tocolytics were used.

Indication B

All first trimester selective termination procedures were performed following an abnormal result obtained by chorion villus sampling (CVS). Second trimester terminations followed either an abnormal karyotype from amniocentesis or an ultrasound diagnosis of a fetal structural anomaly. The abnormal fetus was identified utilizing: 1) drawings from the time of the prenatal diagnostic procedure; 2) the presence of a detectable structural malformation; or 3) fetal sex if discordant and ultrasonically discernible. First trimester terminations were performed as described above. For second trimester procedures, a 22-gauge spinal needle was inserted directly into the fetal heart and 0.5 cc increments of KCl were injected until asystole resulted. One half to 3.0 cc of KCl solution were required to cause cessation of fetal heart activity. All

pregnancies were rescanned 30 minutes following the initial injection to confirm asystole, and if cardiac activity was identified, a repeat procedure was performed the same day. In cases in which selective termination was performed for a cytogenetic or biochemical abnormality, a sample of fetal blood and/or amniotic fluid was obtained from the injected fetus and analyzed for confirmation.

FOLLOW-UP MANAGEMENT

Ultrasound scanning was performed one week following all procedures. After first trimester procedures, scanning was repeated at 16 weeks gestation. Patients were followed to term by their primary obstetrician and contacted by our center at the time of delivery. No coagulation studies were obtained following first trimester reductions but these were obtained weekly following procedures performed at 16 weeks gestation or later. Blood for maternal serum alpha-fetoprotein (AFP) determination was drawn at the time of the 16-week follow-up scan.

RESULTS

Population

Forty-six selective terminations were performed. Thirty-four were reductions of multifetal pregnancies for Indication A, eight were selective terminations of congenitally abnormal fetuses for Indication B and four were performed for Indication C.

Indication A. Table 1 describes the 34 pregnancies referred to our center following infertility treatment elsewhere. Pergonal, either alone (12) or in combination with metrodin(2), lupron(2) or clomid(1) accounted for 50% of

TABLE 1. Selective Termination of Multifetal Pregnancies (N = 34) to Improve Perinatal Outcome and Enhance the Likelihood of the Birth of a Healthy Term Newborn (Indication A)

Reduction to:	Initial No. Fetuses	No. Cases	Gestational Age at Termination (wks)	Ovulation Induction*
Triplets	5	1	11	P-1
Twins	6	3	10, 11-2	P-2, I-1
	5	3	10, 11, 12	P-2, L&M-1
	4	11	10, 7-11, 3-12	P-3, I-1, G-4, C-1, P&M-2
	3	14	1-9, 3-10, 6-11, 2-12, 2-13	P-4, I-4, G-2, P&C-1, P&L-2, M-1
Singleton	3	1	13	G-1
	2	1	12	C-1

*P = Pergonal, I = IVF, G = GIFT, L = Lupron, M = Metrodin, C = Clomid.

the pregnancies in this category. In vitro fertilization was involved in six cases (17.6%) and gamete intrafallopian transfer in seven (20.6%).

One selective termination was performed at 9 weeks, 12 at 10 weeks, 11 at 11 weeks, 8 at 12 weeks and 2 at 13 weeks. The selective termination resulted in one set of triplets, 31 twins and two singletons. Of the two pregnancies reduced to singletons, one was a twin gestation within an abnormally shaped uterus of a woman who had been exposed to DES in utero. This patient's previous singleton pregnancy had resulted in premature labor and delivery. The other was a triplet pregnancy containing monochorionic, monoamniotic twins plus a single third embryo. In this case, the monoamniotic pair was terminated because of the significant perinatal morbidity and mortality of monoamniotic twins, as well as the risk that termination of one fetus from the monochorionic pair presented to the remaining fetus.

Indication B. Eight pregnancies had selective termination for a fetal abnormality and are outlined in Table 2. Four procedures were performed in the first trimester for discordant CVS karyotype results. Three twin pregnancies were reduced in the second trimester; two following abnormal amniocentesis results and one because of a significant fetal malformation identified by ultrasound. One triplet pregnancy was reduced to twins at 16 weeks gestation following the ultrasound diagnosis of a thanatophoric dwarf. In three of the eight pregnancies in this group, the fetus occupying the sac directly above the cervix was affected and terminated.

Indication C. Four pregnancies, three twins and one triplet gestation, had a first trimester reduction to a singleton for this indication (Table 3). All patients were firm in their decision to terminate the entire pregnancy if no

TABLE 2. Selective Fetal Reduction of Multifetal Pregnancies (n = 8) to Allow the Birth of a Healthy Newborn without the Birth of a Co-Existing Fetus with a Congenital Abnormality (Indication B)

Reduction to:	Initial No. Fetuses	Gestational Age at Termination (wks)	Indication	Outcome*
Twins	3	16	Thanatophoric dysplasia	>37 wks AGA
Singleton	2	12	CVS-trisomy 21	33 wks SGA
	2	13	CVS-trisomy 18	>37 wks AGA
	2	13	CVS-trisomy 9	>37 wks AGA
	2	14	CVS-45, X	14 wks preg loss
	2	20	Amnio-trisomy 18	>37 wks AGA
	2	19	Amnio-trisomy 21	>37 wks AGA
	2	17	NTD & hydrocephalus	32 wks, ROM, chorioamnionitis

*AGA = appropriate for gestational age.

TABLE 3. Selective Fetal Reduction of Multifetal Pregnancies (N = 4) to Preserve a Singleton Pregnancy (Indication C)

Reduction to:	Initial No. Fetuses	Gestational Age at Termination (wks)	Ovulation Induction**	Outcome
Singleton	3	11	P	> 37 wks
	2*	10	P	> 37 wks
	2	11	None	> 37 wks
	2	11	C	> 37 wks

*Initially triplets with spontaneous demise of one embryo prior to procedure.

**P = Pergonal, I = IVF, G = GIFT, L = Lupron, M = Metrodin, C = Clomid.

procedure was performed and were counseled extensively on at least two separate occasions. Each of these patients felt that it was her right to determine how many fetuses she would carry.

Immediate Complications

In two of the 42 first trimester cases, and in one of the four performed in the second trimester, ultrasound scanning 20 to 30 minutes following the procedure identified fetal heart activity despite certain asystole of at least two minutes duration at the time of initial injection. In each of these cases, reinjection was successful.

Short-term Complications

There were no infectious or hemorrhagic complications following the selective terminations although one patient had a single episode of vaginal bleeding two weeks after the procedure. There were no coagulopathies. All pregnancies having a first trimester selective termination and a 16-week AFP determination demonstrated significantly elevated AFP values [16].

PREGNANCY OUTCOME

Table 4 demonstrates the outcomes of pregnancies undergoing selective termination. Of the 13 pregnancies reduced to singletons, there was one spontaneous abortion. A 10 week CVS was performed in a monochorionic twin gestation from which only a single sample was retrieved. The direct preparation revealed a 46,XY karyotype while the culture demonstrated a 45,X/46,XY mosaic (50%). A 12 week ultrasound demonstrated a cystic hygroma surrounding one fetus. An amniocentesis performed at that time revealed a 45,X karyotype of the fetus with the cystic hygroma while the initial 15 counts for the co-existing fetus were all 46,XY. Selective termination of the abnormal fetus was performed at 14 weeks gestation without difficulty but was followed 48 hours later by the spontaneous demise of the 46,XY fetus. Ultimately,

TABLE 4. Summary of Fetal Outcome Following Selective Fetal Reduction

	Triplets No. fetuses	Twins No. fetuses	Singletons No. fetuses
Pregnancy continuing	0	0	0
Deliveries			
>37 weeks	0	34 (3)	9
34-37 weeks	0	26 (3)	1
28-34 weeks	0	2	2 (1)
<28 weeks	3	0	0
SAB <24 weeks	0	2	1*
Neonatal deaths	2	0	0

*Chromosomally abnormal.

()—Number of small for gestational age neonates.

further counts from the original amniotic fluid culture and both direct preparation and tissue culture of chorionic villi from the products of conception showed the ultrasonically normal embryo to have a 45,X/46,XY mosaic karyotype.

Of the remaining 12 singleton pregnancies, 10 have delivered full term, appropriate for gestational age neonates. One singleton pregnancy, having a first trimester termination of a co-existing trisomy 21 fetus, was induced for abnormal antenatal testing at 33 weeks gestation. A 1230 gm small-for-dates neonate was delivered and did well in the nursery. A twin gestation in which the fetus overlying the cervix had a lumbosacral meningocele and hydrocephalus was terminated at 17 weeks gestation. At 32 weeks, premature rupture of the membranes of the previously terminated affected fetus led to chorioamnionitis and subsequent preterm delivery of the co-existing 1636 gm baby who did well in the nursery.

Among the 32 pregnancies reduced to twins, there was one spontaneous abortion. Following a 10 week reduction of quadruplets, the twin pregnancy continued uneventfully until 19 weeks gestation at which time the patient presented with silent cervical dilatation, premature rupture of the membranes, and spontaneous passage of the lower fetus. Twelve hours later a second nonviable fetus delivered. Of the twin neonates, 34 were term, 16 delivered between 36 and 37 weeks, 10 delivered between 34 and 35 weeks, and one set of twins delivered at 30 weeks gestation.

The adverse outcome often associated with multifetal gestations of three or more is demonstrated in the only pregnancy reduced to triplets. The patient developed preterm labor unresponsive to tocolytics at 27 weeks gestation. Two neonates died from complications of prematurity and the third, at six months of age, remained on a mechanical ventilator with a confirmed intracranial hemorrhage.

Of the 77 delivered fetuses, seven (9.8%) had weights less than the tenth percentile when plotted on the Lubchenco curve for singleton gestations [16].

DISCUSSION

Clinical Issues

Selective termination of multifetal pregnancies has been described using various techniques including air insufflation [7, 10, 11], fetal exsanguination [12], transcervical aspiration [3], and hysterotomy [2, 13]. Initial reports involved predominantly second trimester procedures aimed at selectively terminating genetically abnormal fetuses [7, 10–13]. More recently, first trimester techniques to reduce high-order multifetal pregnancies have been described [1, 3]. Our study utilized ultrasonically guided fetal injection of a cardiotoxic agent, potassium chloride, for both first and second trimester procedures. Only a small amount of KCl, usually less than 1cc, was required for a first trimester reduction and less than 3cc for a second trimester procedure. Asystole resulted rapidly and the fact that the fetal heart remained well visualized allowed accurate confirmation of fetal death. The technique is technically simple, has been successful in all reports to date, and presents little risk to the woman since the amount of KCl required (2 to 6 meq) is minimal.

Following injection and a confirmed period of cardiac asystole, subsequent recovery of normal cardiac activity was seen in three of our cases and has been reported by others [1]. To avoid the significant potential for damage in a surviving injected embryo, repeat scanning to confirm asystole was performed 20–30 minutes following the procedure and the fetus reinjected when cardiac activity was identified. Reinjection on the same procedure day appeared to be safe, allowed certain identification of the injected fetus, and eliminated the maternal anxiety and psychologic trauma generated by delaying.

In our series, all first trimester selective terminations were performed beyond nine weeks gestation. Although transvaginal reductions have been described at a significantly earlier gestational age [14], such procedures risk unpredictable spontaneous loss of some or all of the remaining embryos. In addition, experience with the “vanishing twin” syndrome [17], as well as our own experience with early pre-CVS ultrasounds [18], demonstrates that background fetal loss drops as gestational age progresses. Delaying beyond 10–11 weeks, however, does not seem warranted since little risk of further spontaneous loss remains and theoretically could be hazardous. This is especially true if three or more embryos are to be reduced, since more degenerating tissue would be retained.

Short-term complications following the procedure were rare. The only consistent finding was an elevated maternal serum AFP which lasted well into

the second trimester and made neural tube screening impossible by this method. Our series confirms the low probability of a maternal coagulopathy secondary to retained fetal products. Despite the low risk of this occurrence, coagulation screening following second trimester procedures still seems justified until further data are collected [19, 20]. Since such occurrences have not been seen following either spontaneous or induced first trimester procedures, monitoring coagulation factors in these cases may not be necessary.

Selective termination of a fetus with a congenital abnormality presents additional issues. In all such cases, identification of the affected fetus is required, sometimes weeks following the initial diagnostic procedure. In terminations for a structural abnormality, or in cases in which discordant sex is ultrasonographically demonstrable (usually after 18 weeks gestation), this problem is minimized. In first trimester cases, our experience shows that a detailed drawing, including fetal and placental location, at the time of the CVS procedure will correctly demonstrate the location of the affected fetus up to three weeks later. It must be cautioned, however, that orientation can change, and confirmatory cytogenetic or biochemical studies at the time of the reduction are mandatory. If identification is at all uncertain, further diagnostic testing by either cordocentesis, placental biopsy, or amniocentesis should be performed *prior* to termination.

Selective termination of a fetus with a *lethal* malformation is only indicated if such a defect presents greater hazards to the co-existing pregnancy than does the risk of termination. For example, we evaluated a triplet pregnancy containing a fetus with thanatophoric dysplasia. Although the lethality of this malformation is certain, selective termination potentially improved the outcome by eliminating the probability of significant polyhydramnios and pre-term delivery [21].

In monochorionic pregnancies, the need for selective termination will usually involve the second trimester diagnosis of a structural malformation. In certain rare circumstances, such as the case described in our series, a cytogenetic discrepancy may be identified in the first trimester. To date, all but one attempt at selective termination in a monochorionic pregnancy [2] have led to demise of the co-existing fetus within a short period. The only successful case employed surgical removal of the affected fetus [2]. Furthermore, even if demise does not occur, a real danger of embolic damage to the surviving twin exists [22-26]. Present experience would therefore indicate that in cases of potential fetal anastomoses, selective termination will result in demise or damage of the coexisting twin unless the joined circulation is interrupted. For this reason, we believe that a monochorionic pregnancy represents a contraindication to selective termination unless the abnormal fetus is removed, a procedure reported infrequently and one whose risks have not been evaluated.

Terminating the fetus overlying the internal cervical os has the theoretic risk of rupture of the degenerating sac leading to ascending infection. Although we attempted to avoid the lower sac in all cases, the presence of a fetal abnormality required such a procedure on three occasions. In one of these, membrane rupture and chorioamnionitis of the degenerating sac occurred at 32 weeks gestation. More experience is required to evaluate the relative risks, but when feasible, the lower sac should be left intact.

Selective terminations were performed with the ultimate goal of prolonging pregnancy and decreasing the morbidity and mortality associated with preterm delivery. This was successfully accomplished in our series with the only neonatal mortality and significant morbidity occurring in the multiple gestation reduced to triplets.

Despite the fact that there is general agreement that adverse perinatal outcome is directly related to the number of fetuses (Table 5), there is much debate concerning both the number of fetuses needed to justify reduction and the appropriate number of fetuses to leave. Berkowitz et al [1] have suggested that women with four or more fetuses are appropriate candidates for selective termination. Recently, Newman et al [28] have shown a significant improvement in the perinatal mortality rate for triplets utilizing modern neonatal and perinatal technology. This improved survival, however, was due in large part to neonatal advances since the average gestational age at birth was 33.6 weeks and only 4.5% delivered after 37 weeks. Over 20% delivered before 32 weeks and despite a goal of outpatient management, 44.4% required antepartum hospitalization. Consideration of this question, therefore, cannot be limited to the perinatal mortality rate alone; other considerations such as morbidity, long-term outcome, costs (both financial and psychologic) and societal and ethical issues deserve thorough evaluation. Unfortunately, most of these questions remain unanswered since the literature contains few large contemporary series of triplets or higher order multiple gestation that evaluate these factors. At present, a prospective registry has been developed to more accurately evaluate the natural history of high-order multiple gestations which will allow better quantification of the risks and benefits. At present, the decision should rest with the pregnant woman after thorough non-directive counseling.

Although twins present perinatal hazards, in almost all cases the risks are manageable and the outcomes good enough that reduction to a singleton on medical grounds alone is not warranted. However, there are couples with unusual medical circumstances or compelling social and psychologic indications for whom reduction to singletons should be considered. In two pregnancies in our series, reduction to a singleton was proposed for medical indications with the intent of improving pregnancy outcome. In both cases, after extensive counseling, the couple chose this option. Four of the pregnancies in our series were reduced to singletons for other than straightforward obstetric indica-

TABLE 5. Pregnancy Outcome of Published Series of Multiple Gestations

Study	# Fetuses	# Cases	Deliv < 28 wks		28-31 6/7 wks		32-36 6/7 wks		≥37 wks		PNM	Refer. #	Dates
			#	%	#	%	#	%	#	%			
Persson	Twins	136	0	0	4	2.9	30	22.1	102	75	44.1	30	1973-78
Savona-Ventura	Twins	190	8	4.2	10	5.3	44	23.2	128	67.4	100	31	1983-85
Keith	Twins	588	29	4.9	35	6.0	131	22.3	372	63.3	72	32	1971-75
Medearis	Twins	2831	105	3.7	145	5.1	800	28.3	1781	62.9	116	33	1972-76
Caspi	Twins	21	3	14.2	2	9.5	7	33.3	9	42.9	166	34	1968-75
Total for	Twins	3766	145	3.9	196	5.2	1012	26.9	2392	63.5	106		
Michelwitz	Triplets	15	1	6.7	0	0	12	80.0	2	13.3	133	35	1954-76
Holeberg	Triplets	31	5	16.1	6	19.4	16	51.6	4	12.9	312	36	1960-79
Itzkowic	Triplets	59	6	10.2	9	15.3	29	49.2	15	25.4	232	37	1946-76
Daw	Triplets	14	1	7.1	0	0	8	57.1	5	35.7	309	38	1958-77
Caspi	Triplets	5	0	0	2	40	3	60	0	0	200	34	1968-75
Syrop**	Triplets	20	3	15.0	12	60	12	63.2	5	25.0	216	28	1946-83
Ron-El**	Triplets	19	7	36.8							185	39	1970-78
Total for	Triplets	124	13	10.5	17	13.7	68	54.8	26	21.0	247		
Ron-El*	Quads	6	0	0	2	33.3	1	16.7	3	50	185	39	1970-78
Caspi*	Quads	3	1	33.3	1	33.3	0	0	1	33.3	583	34	1968-75
Total for	Quads	9	1	11.1	3	33.3	1	11.1	4	44.4	318		

*Note: May be overlapping. Studies from same hospital with overlapping periods (1970-75).

**Not included in totals because gestational age at delivery not compatible with other series.

tions. In each of these cases, the couple, after thorough counseling, felt that this was the appropriate reproductive option for them. Each couple had anticipated and, in three cases, actually scheduled termination of the entire pregnancy if reduction was not available. We do not wish to imply that reduction to a singleton gestation for other than medically justifiable reasons should be taken lightly. However, as long as women have the legal option to choose their own reproductive future and, as long as society accepts elective first trimester pregnancy termination as a woman's right, it may be appropriate to utilize this technology in selected cases.

Counseling Issues

Patients referred for fetal reduction are all in a time of crisis. The indication for fetal reduction often plays a significant role in their outlook both toward the pregnancy and toward the procedure. Patients referred for Indication A have been through lengthy fertility treatments and have been on an emotional roller coaster since treatment began. They are elated when the pregnancy test is positive but this elation often fades when the first ultrasound reveals a multifetal pregnancy.

They express anger and frustration at 'medicine' in general and feel that 'medicine' caused the problem and must now solve it. Many also express guilt at contemplating fetal reduction and the intentional termination of a fetus or fetuses. Many couples question the level of "consciousness" that the remaining fetuses have and wonder if the remaining fetuses somehow know that one of their potential sibs was terminated. These couples wonder if children who remain will, as they grow, be a constant reminder of the fetuses that were terminated.

Many patients are uncertain about this decision because there is no absolute way of predicting whether their multiple pregnancy would carry to term or deliver prematurely. Ultimately, after discussing the available options, with a genetic counselor, with the perinatologist who would perform the procedure and with their fertility specialist, patients must make a decision and usually express relief after it is made. If they decide to reduce the pregnancy, the relief is often delayed until the procedure itself is over. With every subsequent ultrasound and obstetric appointment these patients seem to become less anxious and gradually adjust to the pregnancy as it progresses.

Patients who had fetal reduction for Indication B respond similarly to patients faced with a singleton pregnancy which is found to be chromosomally or structurally abnormal [41]. They are often less angry than the Indication A patients but feel the guilt and inadequacy of producing a less-than-perfect fetus. Most of these patients have felt relatively positive about fetal reduction because it allows the preservation of the unaffected co-twin. When counseling patients who are having prenatal diagnosis for twins, it is important to

mention the possibility of fetal reduction to make the patient aware of all available options.

The anxiety expressed by these patients often relates to the possibility of inadvertently terminating the unaffected fetus. This has not occurred in our series but the patient must be apprised of this risk. This concern is usually alleviated upon receipt of confirmation studies done at the time of reduction. These patients will also express relief after the procedure and their level of comfort with their decision grows as does the pregnancy.

Patients referred for Indication C are rare. These are patients who, for unique social or personal reasons, are opposed to carrying a multiple pregnancy. Some of them have other small children requiring attention, some feel financially unable to add two more children to their household. These decisions are seldom made lightly by the patients themselves. After extensive counseling, comparing the relative risks and benefits, these patients decided to have a fetal reduction to a singleton. Counselors and physicians tend to be less comfortable with this group because there is no medical imperative for providing the procedure. However, it is not the genetic center staff's role to make these decisions for the patient. Legally, at least for today, *Roe v. Wade* [40] permits pregnancy termination prior to 24 weeks gestation for any indication. Should fetal reduction from twins to singletons be any different? In answering this question a number of moral, ethical and practical considerations must be taken into consideration: 1) patient autonomy, 2) fetal rights, 3) scarcity of resources, 4) risks to remaining fetus and 5) physician and counselor moral autonomy.

CONCLUSION

The authors have demonstrated in this series that selective termination can be performed safely with minimal risk to the remaining fetuses. The authors believe that selective termination for the indications herein described is an alternative for the management of multifetal pregnancies and that there are no public policy obstacles to offering this alternative to pregnant women. The counseling provided to these patients must be thorough and non-directive, encouraging the couples to choose between the possible alternatives.

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Medical, Legal and Psychologic Considerations in Gamete Donation Social Issues Committee Workshop

Reviewed by Shane Palmer, MS, and Joanne Malin, MS

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INTRODUCTION

Due to recent advances in reproductive technologies, as well as controversy regarding the “rights of embryos,” the Social Issues Committee felt compelled to conduct a workshop on gamete donation. Medical, legal and psychologic aspects all have implications for individuals and couples pursuing these new procedures. It is predicted that our future caseloads will include infertile or at-risk couples who may choose these options—thus, it is necessary for all of us to become more knowledgeable in this area.

The following summary reviews the presentations of each of our distinguished speakers.

MEDICAL ASPECTS

**Presented by David K. Walmer, MD, PhD,
Duke University Medical Center**

Infertility may be considered a disease, if disease is defined as an impairment of the vital functions of the living body or any of its components in response to environmental factors or due to inherent defects of the organism. Loss of gametes may result from exposure to environmental agents such as X-rays, cigarette smoke, and heavy metals. Inherent defects of the organism include gonadal dysgenesis, cystic fibrosis, and gonadal tumors.

Adoption vs Gamete Donation

Gamete donation has several advantages over adoption. Waiting lists at adoption agencies may be quite long and very often, older couples may have a slightly more difficult time in finding available children. Finally, gamete donation does allow a couple to experience the pregnancy, the birth and for the woman – nursing.

History. The history of gamete donation can be traced back to its use in animal husbandry. Artificial insemination in animals was first used to adversely affect the enemy's horsebreeding in times of war. The first recorded embryo transfer in an animal was accomplished in 1890 and reported in the *Proceedings of the Royal Society of London*, 48:457 by Heape [1]. The first recorded artificial insemination by husband was completed circa 1775 in London by John Hunter, MD, because the man had hypospadias. This procedure was carried out in secret and only recorded in Dr. Hunter's personal diary [2]. By the mid-1880s, artificial insemination by donor was being utilized.

In 1983, Buster completed the first successful nonsurgical recovery and transfer of ova [3]. In 1984, two landmark articles were published in *Nature* [4]. One described hormone replacement therapy to synchronize women's cycles for oocyte donation. The second described the first pregnancy achieved by oocyte donation. According to a 1989 article published in *Fertility and Sterility* [5], 60 donor oocyte transfers were attempted in 1987. The fecundity rate was 20%.

Indications. Indications for gamete donation vary, but may include the following situations in men: noncorrectable ejaculatory dysfunction, genetic abnormalities, and oligo/azospermia. Indications for women include: severe Rh-isoinmunization when the partner is Rh-positive, ovarian failure secondary to genetic syndromes, and autoimmune diseases. In addition, some couples choose gamete donation because of their increased risk to have a child with a genetic condition. As in the case where each partner is a carrier for an autosomal recessive disease, or when one partner has a dominant genetic syndrome.

Screening procedures for gamete donation. In 1986, Greenblatt et al [6] published an article in *Fertility and Sterility* describing guidelines for screening donors for sexually transmitted diseases. They pointed out that semen can transmit a variety of viral pathogens, including hepatitis B, cytomegalovirus (CMV), and the retrovirus associated with AIDS. Herpes simplex virus (HSV) and human papilloma virus (HPV) are known to infect the urethra and might be transmitted via semen, although HSV is rarely isolated from semen in the absence of overt herpetic lesions. Also reported in the medical literature are transmission of *Neisseria gonorrhoeae* and *Chlamydia trachomatis* via donor insemination. Spermatozoa have been considered a possible vehicle for both of these pathogens into the upper genital tract of women [6].

Treponema pallidum and bacterial agents of lower or uncertain pathogenicity, such as Group B streptococcus, *Ureaplasma urealyticum*, *Mycoplasma hominis*, and *Gardnerella Trichomonas vaginalis* are undoubtedly common contaminants of semen from donors [6]. *Trichomonas vaginalis*, a protozoan which is sexually transmitted, can also be found in the urethras of asymptomatic men [6].

Sexually transmitted pathogens are associated with a wide variety of disease states in women. In pregnancy, complications include spontaneous abortion, chorioamnionitis, premature rupture of membranes, premature delivery, stillbirth and perinatal death, as well as congenital and perinatal infections and postpartum endometritis [6]. Dr. Walmer reviewed the following recommendations for screening semen donors and recipients. The initial screening process should include a complete history and CMV testing even in those with a negative history. A physical examination should follow, including a genitourinary (GU) evaluation for condyloma, urethritis, vesicles or ulcers. A GU culture for *Gonorrhoeae* and *Chlamydia* should be done, along with serology for HIV, syphilis and hepatitis B. Optional testing may include GU culture for mycoplasmas and Group B streptococcus.

Dr. Walmer also suggested minimizing the number of donors per recipient, and using intrauterine insemination only when indicated. It is also important to screen each recipient and spouse as thoroughly as the donors, and to keep health records on the recipients and donors. If semen is frozen, the screening may be accomplished in one visit. As of February 1988, the American Fertility Society and the Centers for Disease Control guidelines recommend freezing semen for six months and confirming seronegativity for HIV before using semen. Vertical transmission to infants has been documented in spontaneous vaginal deliveries and C-sections and also from nursing mothers with AIDS. The screening on the initial visit may be accomplished by a history and physical examination along with the collection of semen and serum for serology and culture studies.

The issue of screening semen donors for genetic disorders has been addressed by Verp et al (1983) [7]. AID screening by Verp's group was accomplished by medical and family history taking. Karyotyping, pedigree analysis or metabolic screening were not done. Donors for artificial insemination were excluded for the following reasons: serious mendelian disorders in first- or second-degree relatives, severe multifactorial disorder in the donor, and spontaneous abortion or stillbirth of donor's offspring. Donors of Eastern European Jewish ancestry were screened for Tay-Sachs disease and black donors for sickle cell disease heterozygosity. Potential donors with fewer than 80 million sperm/ml, less than 70% motility or less than 70% normal morphology were excluded; only 10% fell into one or more of these categories. The American Fertility Society 1986 guidelines recommend volume greater than 2 ml, motility greater than 60%, concentration greater than 50 million/ml and morphology greater than 60% normal. In this study, there was no increase in birth defects over general population risks. However, the numbers were low—119 liveborn infants were born using sperm from 30 donors. Two newborns out of 119 were born with congenital malformations.

Oocyte Donation

In order to retrieve oocytes, the timing of the cycle needs to be precise. This is accomplished by Basal Body Temperature charts, urine LH kits, ultrasound, and hCG administration to produce an iatrogenic LH surge. The donor and recipient must be synchronized with fresh oocytes/embryos. The techniques for preparing the recipient include a pituitary down regulation with a GnRH analog and estradiol and progesterone replacement. The Norfolk regimen is the most widely used method.

For the donor, a superovulated cycle is created by human menopausal gonadotropin (hMG) and monitored by ultrasound to determine the time of oocyte retrieval. In Rhesus monkeys, there is a tolerance of three days of asynchrony between the embryo and the endometrium in estradiol and progesterone ova replacement cycles. In humans, the ovum normally arrives in the endometrial cavity four or five days after the LH surge [8].

Luteal Phase Support. Estradiol and progesterone replacement are given to patients with premature ovarian failure. Adequate luteal function is anticipated within 50–60 days.

Summary

In summary, the most common procedure performed today for gamete donation is donor oocyte retrieval in which the recipient undergoes in vitro fertilization, gamete intrafallopian transfer, or pronuclear stage embryo transfer (IVF/GIFT/PROST) etc in the hope that a pregnancy will ensue. Guidelines for semen collection have been established and published by the American Fertility Society. Also, guidelines and techniques for oocyte donation have been established. These new reproductive technologies offer some infertile or at-risk couples the experience of pregnancy, and, therefore, have advantages over adoption.

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LEGAL ASPECTS

**Presented by Estelle Rogers, JD
Washington, DC**

Ms Rogers, a practicing attorney in Washington, DC, has three pending cases on pro-choice rights to present to the U.S. Supreme Court. She reviewed recent court cases that have received significant media attention during the last few months. One issue involves the "rights of embryos." A recent court decision in Tennessee awarded custody of embryos to the mother with pending visitation rights for the father, should a pregnancy come to term. The most shocking aspect of this ruling was that the judge determined that the judicial system would decide whether or not to implant the embryos into another woman if the mother decided not to use them. It is not yet clear where the rights of the biologic parents begin and end.

Also discussed was the process of "contracting." The term is familiar to genetic counselors who may state goals and objectives prior to each session. In most situations involving surrogate mothers or gamete donation, contracts are arranged and all parties involved are satisfied with the terms and outcomes. However, in some situations, this is not the case. Therefore, thorough contracting is important in matters involving gamete donation. Decisions should be made regarding disposition of embryos should death, divorce, or other unforeseen events occur. Transportation of stored gametes or embryos to other centers in the event of patient relocation or dissatisfaction should also be discussed.

Informed consent is another important issue. The physician should inform the couple about risks and benefits. The couple should know whether the procedure in question is still considered experimental. It is important for the health professional to document these discussions, any medications prescribed, and procedures in the patient's medical record. As we are all aware, the medical record is essentially a legal document. It is also the responsibility of the practitioner to discuss his center's success rate, if known. If these data are not available, then the consultands should be made aware that the figures used reflect the national average (Andrews, 1987).

A person cannot be financially reimbursed for donating gametes. However, many programs skirt this issue by paying for the client's time or discomfort.

Although the medical advances allow infertile couples alternatives for

childbearing, they have also opened up a relatively new and unexplored legal battleground.

LEGISLATIVE ISSUES

Presented by Shane M. Palmer, MS, based on information from Jerry Mande, Senior Legislative Advisor to Senator Albert Gore

Senator Gore (D-Tenn) is Chairman of the Consumer Subcommittee. In a 1988 letter addressed to the Honorable Frank E. Young, MD, PhD, Commissioner of the Food and Drug Administration, Senator Gore stated that donated sperm and eggs are considered consumer products. Also in 1988, Senator Gore proposed legislation to set up standards regarding gamete donation. He was shocked to learn the results of a survey conducted by the Office of Technology Assessment, which found that fewer than half of physicians/health care providers screened donors for genetic diseases. Many physicians performing the procedures appeared not to comprehend basic genetic concepts. As Senator Gore states, "... it is often easier to learn whether a prospective donor plays the cello than whether there is a family history of Huntington's Disease." He adds that Thomas Jefferson stated that "our laws and institutions must move forward hand in hand with the progress of the human mind." Science has progressed dramatically while public policy has remained at a standstill.

In 1985, Senator Gore addressed this issue in a letter to the U.S. Congress. He assisted in establishing the Biomedical Ethics Board as a forum to help develop policies in this expanding area of science.

Senator Gore has recommended the following in order to assure safe gamete donation:

- 1) Establish a National Data Bank to store medical and gamete histories of anonymous donors. Identity of donor will remain confidential. However, offspring should not be denied basic information about their genetic or medical past.
- 2) The Food and Drug Administration should act immediately to ensure that the same precautions that have made the blood supply safe are applied to artificial insemination samples.
- 3) The government should assist professionals involved in artificial insemination to develop a system of quality assurance.

The Senator strongly recommends that the government do more to make sure that individuals seeking these services receive care and treatment based on the best possible medical sciences and not the "best guesses" of inadequately trained professionals.

PSYCHOLOGIC EFFECTS

Presented by Mindy Schiffman, PhD
IVF—Australia
Port Chester, NY

The psychologic consequences of both infertility and “being-at-risk” for having a child with a genetic disease must not be ignored. Couples will often experience shock, denial, anger, confusion, and depression. Genetic counselors need to approach these issues with their patients.

Dr. Schiffman emphasized the concepts that genetic counselors have always advocated. We must encourage and allow our couples to grieve over their loss. Quick decisions regarding a particular course of action should be discouraged. The information needs to be integrated in order to make decisions which are most appropriate.

One course of action that a couple may choose in response to either infertility or “being-at-risk” for having a child with a genetic disorder is gamete donation. Inherent in this option is the difficult thought process which a couple must entertain. How do we choose the donor? Will either of us have any resentments following the baby’s birth? Should we tell our child about his/her conception? And if we should, will we? As genetic counselors, we need to help our patients explore these questions as individuals and as a couple.

It is also crucial to be able to distinguish which couples may be at risk for coping problems. Several clues that Dr. Schiffman identified were:

- prior psychiatric history
- prior history of drug or alcohol abuse
- insular couples—those that have few resources
- marital conflict or couples who have differing attitudes and goals
- major depressive symptoms (or other major psychiatric disorders)

There are times when a genetic counselor will need to refer a couple to a psychologist or psychiatrist. It is important to be able to recognize one’s limitations in dealing with some of the deeper psychologic issues surrounding infertility or genetic disease. Perhaps a couple should be referred to a peer support group such as RESOLVE, Compassionate Friends or the Adoptive Parents Committee. Two resource books with extensive bibliographies which genetic counselors might find helpful are:

- Menning, Barbara Eck: “Infertility: A Guide for the Childless Couple,” 2nd Ed. New York: Prentice-Hall, 1988.
- Noble, Elizabeth: “Having Your Baby by Donor Insemination: A Complete Resource Guide.” Boston: Houghton Mifflin, 1987.

A SUCCESSFUL GIFT PROCEDURE

**Presented by Reverend and Mrs. Waylan Owens
New Orleans, Louisiana**

The Social Issues Committee felt that it was important to have a couple present their experiences regarding the new advances in reproductive technology. An opportunity to talk with a couple who have had this experience may help sensitize us to the emotional aspects, since we often take for granted our own capacity for childbearing. Infertility, however, is a common problem, not only among our patients, but also among our colleagues, friends and relatives.

Rev. Waylan Owens and Mrs. Betsy Owens were recommended to our workshop's organizers by a genetic counselor at Tulane University Medical Center. Mrs. Owens is a nurse in the Neonatal Intensive Care Unit at that institution. Rev. Owens is presently working on a doctorate in theology. He is a Baptist minister with a small, mostly elderly congregation in the state of Mississippi. Rev. and Mrs. Owens have a seven-month-old son, Blaine, who was conceived through the GIFT procedure.

Mrs. Owens described their situation as similar to a "roller-coaster ride." There were many ups and downs, expectations and disappointments. These feelings are not unique to the Owenses. This is a normal reaction to this sort of situation and couples undergoing new reproductive procedures should be forewarned.

Mrs. Owens felt the need to discuss her situation with her supervisor and colleagues as she worked a 12-hour shift and needed her medication during work hours. There were also times when it was necessary for her to have ultrasounds to monitor ovulation. It was comforting for Mrs. Owens to know that her colleagues were willing to trade shifts, administer her medicine, and cover for her when necessary. She readily admits that she was very fortunate to work with supportive individuals.

Both Rev. and Mrs. Owens felt that prior to proceeding with the GIFT procedure, a couple needs to thoroughly discuss this option and set limitations. They stated that their lives began to revolve around Mrs. Owens' cycle, the ultrasound examinations, the Pergonal injections and the GIFT procedure itself. They rarely took time for themselves. They were so intent on becoming pregnant and following the recommended protocol that even going to a movie was out of the question. Also, given the high cost of this procedure, they were restricted in what they could do for entertainment. Rev. Owens pointed out that a couple could very easily spend their life savings and go into debt and still not be successful. Thus, they strongly suggest that a couple set financial limitations and take time out for themselves. They were able to accomplish these goals because they were very open with one another from the onset.

Both Rev. and Mrs. Owens felt that their spirituality helped them to cope with this ordeal. Their belief is very strong and was a factor in their decision to pursue this option for procreation. Individuals in their religious community were supportive. They saw no conflict between their religious beliefs and pursuit of the GIFT procedure.

ADDRESSES OF INTEREST

The American Fertility Society
2140 11th Avenue South, Suite 200
Birmingham, AL 35205

Resolve, Inc.
PO Box 474
Belmont, MA 02178

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The Role of Ultrasound in Screening for Down Syndrome

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Several studies have suggested that ultrasound may be useful in prenatal screening for Down syndrome (DS). We reviewed our experience with DS between 1983–1988, with two questions in mind: 1) how many DS fetuses had abnormal ultrasound exams, and 2) what value is femur measurement in screening for DS?

Fifty cases were identified between 15 and 20 weeks gestation, all of which had been referred for advanced maternal age or low maternal serum alpha-fetoprotein (MSAFP) levels. Five fetuses (10%) had an abnormal exam: two heart defects, one duodenal atresia, one omphalocele, and one cystic hygroma. Three other fetuses had an echogenic bowel, a finding not previously reported in association with DS. In the DS group, 7/50 (14%) had a ratio of observed to expected femur length ≤ 0.91 , while 33/470 (7%) of the normal population had such a low ratio. If the regression equation reported by Benacerraf et al is used, a ratio of ≤ 0.91 was seen in 26/50 (52%) of DS fetuses and 213/470 (45%) of normal fetuses.

We conclude that ultrasound may have a useful role in screening for DS. However, each center should carefully review its own experience with both normal and DS fetuses before using ultrasound to screen for DS.

What Our Patients Are Reading About Reproductive Technologies A Review of Eight Popular Women's Magazines, 1978 and 1988

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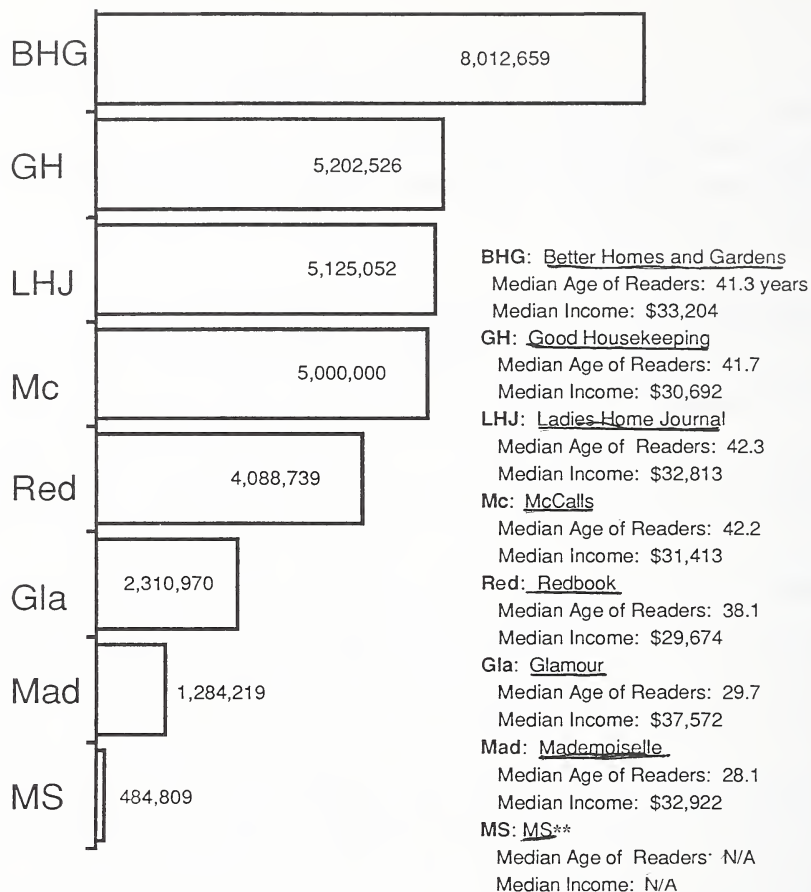
INTRODUCTION

Magazines are an important source of health information for the lay public. As part of the "mass media," the functions of magazines include acting as a social unifying force; providing people with an awareness of new choices; and establishing and reinforcing group norms. As the popular consumer magazines educate, entertain and inform the public, several aspects of health education occur. The Knowledge-Attitude-Behavior model of health education purports that attitude change or knowledge increase precede and predict behavior change. Through the variety of formats available in magazines, the reader may find support for a new belief, another antecedent to behavior change. Or, the reader may identify with the women portrayed in articles who make certain reproductive choices and therefore also choose that behavior.

Genetic counselors often relate anecdotes of increased interest, referrals and client telephone calls following publication of certain articles in "women's magazines." The genetic counselors in Oregon reviewed the coverage of reproductive technology, prenatal diagnosis, infertility, teratogens, abortion and adoption in the 24 issues of monthly women's magazines during the years of 1978 and 1988 for coverage, accuracy and thoroughness (Fig. 1).

The group had two basic hypotheses:

- 1) There would be more articles written on these subjects in 1988 than in 1978 in the selected magazines.
- 2) The material presented in the popular consumer magazines would be inaccurate, incomplete, not substantive and misleading.



** MS halted publication in November, 1989. It will be reintroduced in 1990 in a new format as a quarterly.

Fig. 1. Total paid circulation per month of 8 selected women's magazines

RESULTS

As shown in Table 1, infertility was the most frequent topic covered in 1978. In 1988, infertility remained the number one subject of the seven. By 1988, prenatal diagnosis, teratogens and alternative conception methods had become more common themes. The *MS* article about abortion focused on the politics, not the experience or dilemma of choice. The *Glamour* articles on abortion were less political and more personal. The other magazines surveyed did not address abortion. There were no articles about women who choose not

TABLE 1. Coverage of Topics in 8 Selected Women's Magazines

	BHG 78/88	GH 78/88	LHJ 78/88	Mc 78/88	Red 78/88	Gla 78/88	Mad 78/88	MS 78/88	Total
Infertility	—/—	1/2	—/—	2/1	1/2	4/2	—/—	—/2	8/9 17
Teratogens	—/—	6/6	—/—	—/—	—/—	—/2	—/—	—/—	6/8 14
Alternative Conception	—/—	2/1	2/2	—/—	—/1	—/3	—/—	1/3	5/10 15
Prenatal Diagnosis	—/—	2/—	—/2	—/—	1/4	—/3	—/—	—/1	3/10 13
Adoption	—/—	—/1	—/—	—/—	2/2	—/2	—/—	—/1	2/6 8
Abortion	—/—	—/—	—/—	—/—	—/—	3/1	—/—	7/5	10/6 16
Other Related*	—/2	2/3	—/—	—/—	—/1	1/—	—/—	—/—	3/6 9
Total	—/2	13/13	2/4	2/1	4/10	8/13	—/—	8/12	37/55 92

*Includes coverage of genetic counselors and counseling, gestational diabetes, pregnancies after 34, etc.

to use prenatal diagnostic procedures as reproductive technology. There are no examples about how or why families make decisions when prenatal diagnosis reveals an unwanted condition.

The articles presented the subjects in a positive fashion. The stories usually were "happy," rather than depressing. All of the magazines have health-oriented columns or features each month. *Mademoiselle* did not cover any of the chosen subjects in 1978 or 1988. *Better Homes and Gardens* had poor coverage in its two 1988 articles.

The remaining six magazines had accurate and nearly complete coverage of topics they published in 1978 and 1988. The negative aspects of procedures, technologies and choices were usually missing in the articles.

RECOMMENDATIONS

- 1) Genetic counselors should review articles in consumer magazines brought to their attention by patients, in order to build upon correct information and supply missing information.
- 2) Genetic counselors should be aware of the quality of articles in the magazines on these health subjects in their waiting rooms.
- 3) Genetic counselors should write letters to the editors of consumer

magazines to correct misinformation and missing information. Telephone calls to the editorial boards are also an option.

- 4) Genetic counselors should consider submitting articles and stories on these topics to popular consumer magazines, as well as be available to the media for interviews and background material.

ACKNOWLEDGMENT

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Counseling the Underserved: When an Old Reproductive Technology Becomes a New Reproductive Technology

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UNDERSERVED POPULATIONS

Recent advances in reproductive genetics and new technologies for their application are having a profound effect on the possibilities for prenatal diagnosis. The dazzling accumulation of information in molecular genetics holds out hope for rapid progress in screening, diagnosing, and eventually ameliorating genetic diseases. Most of the progress in DNA-based prenatal diagnosis will occur in the private sector, serving relatively small numbers of people, such as those whose families are at high risk for genetic diseases like Huntington disease, neurofibromatosis, and cystic fibrosis, as well as those insured for exceptional medical testing. The new DNA technologies hold out the possibility of great benefits for affected families, but they are unlikely to have widespread impact on mass prenatal screening today. For the vast majority of Americans, prenatal diagnosis means the continued routinization of amniocentesis, and the increasing use of chorionic villus sampling.

Although amniocentesis has become an accepted part of prenatal care for middle-class professional women and their families, we believe its availability and utilization are changing dramatically. We initially hoped to present information on the increasing rate of amniocentesis utilization over the last decade, tracked by income, race, ethnicity, payment plan or any other available indicators to show which social groups are still relatively underserved. We then wanted to compare amniocentesis utilization rates with the shifting demography of the new immigration in the same time period. But such data simply do not exist. To understand why, we would like to describe the paper chase which we followed in our own research.

In speaking with researchers at the Center for Disease Control, the Office of Technology Assessment, the Office of Maternal and Child Health, the March of Dimes, the American College of Obstetricians and Gynecologists, the

various CORN regional and national networks, the Bureau of Vital Statistics, as well as with outstanding academic epidemiologists and biostatisticians concerned with prenatal services, it became clear that at least two factors account for our lack of information. One is the inherent difficulty of collecting and linking the necessary data. Ideally, cytogenetic laboratory reports and birth certificates must be monitored nationally and a large group of maternal questionnaires must also be sampled. The 1988 National Maternal and Infant Health Survey administered through Vital Statistics is collecting these data and results are expected in about one year.

The Federal Government was just beginning to prepare to monitor prenatal screening in the late 1970s, when the second confounding factor arose. That factor is block-grant funding for maternal and child health services, including genetic services, instituted in 1981. In returning 85% of Federal MCH funds to the states, Congress enjoined the Federal Government from collecting evaluative statistics on how the monies were being spent. Only some states monitor prenatal genetic services. The regional genetics networks are quite varied in their abilities to collect data from participating centers. In summary, the Federal Government has chosen not to know. The impact of that stance on planning, outreach and provision of genetic services is sobering.

A 1980 study at the National Center for Health Statistics sampled just under 5,000 amniocentesis reports. This study suggested that white mothers over 35 were using this test 30% of the time, while black mothers had a 17% utilization rate. The study cautioned that the numbers for black women were unreliable because the records of so few were sampled [1].

When discussing advances in prenatal testing, 1980 sounds like ancient history. Statistics from New York State and New York City suggest that as late as 1985, the single best predictor of whether a pregnant woman at/over age 35 would have an amniocentesis remained her county of residence. Utilization rates varied widely across the state from a low of about 5% in some rural counties to a metropolitan high of 50%. In New York City, as of 1988, the model outreach work of the Prenatal Diagnosis Laboratory (PDL) in serving low-income women resulted in about 45% of pregnant women at/over 35 years having the test compared to less than 25% in 1980. PDL's tenth anniversary data indicate that utilization of its services has dramatically increased among Hispanic, African-American and Asian women [2].

Even in the larger metropolitan areas, administrative and economic barriers often prevent underinsured or low-income women and their families from having the choice to use or not use amniocentesis. Poor people, especially if they are recent or undocumented immigrants, lead very complex and stressful lives. A bewildering and often contradictory array of policies for coverage of or reimbursement for laboratory fees, a limit to the number of specific tests certain policies will cover, health maintenance organizations (HMOs) which have contracted with particular labs that do not provide genetic counseling

services, and transportation obstacles are among the many problems that confront potential clients who might benefit from genetic counseling services.

In New York City, where amniocentesis is widely accessible, well-publicized, and a combination of benefits programs makes the test low-cost or free for uninsured, low-income women, less than half the pregnant women at/over 35 use amniocentesis. What accounts for this low utilization rate? The main reason identified by biostatisticians is late entry into prenatal care. Pregnant women new to this country may be unfamiliar with the intimidating, complex and bureaucratic world of hospital facilities and entitlements. Some clinics have long wait lists for intake appointments. A recently immigrated Haitian woman who has had three children in her home village unassisted by any medically trained birth attendants will not necessarily know that she is entitled to "jump the line" and receive early screening if she is over 35, when she finally makes her way through the hospital maze to the prenatal clinic. Her confusion about the rules governing access to prenatal care differs from decisions made by experienced mothers who have given birth to many children in a familiar hospital. In the New York Hasidic Jewish community, for example, women know they must register by the sixth month to insure a bed at the time of delivery, but they are not likely to register in time for early intervention "just because I'm getting older." In many states and cities, prenatal care is also unevenly distributed and sometimes inadequate. Women may fear and mistrust all medical personnel, or at least, the doctors and nurses at their hospital. A low-income Dominican patient answered our follow-up telephone interview after her genetic counseling session, with these words: "I'm damned tired of sittin' in that zoo of a waiting room for three hours for nothin'." She therefore decided against amniocentesis.

It may also seem illogical and dangerous to consider a new, invasive technology. Patients accustomed to traditional Chinese medical systems deploy a sophisticated nosology of the body. Balance and harmony are the goals of good health practices. Bodily fluids are a central concern. To remove fluids from a person who is not sick, especially a pregnant person who is following many practices to maintain physical harmony is tantamount to throwing the body into disequilibrium. Therefore, a woman committed to traditional Chinese health practices may react to the idea of amniocentesis with shock, disbelief and hostility. It requires tact, openness and good communication skills to discuss the implications of the removal of three tablespoons of replaceable amniotic fluid.

COMMUNICATIVE BARRIERS

Possible communicative barriers based on cultural differences can arise at every stage of the counseling process. Genetic counselors and geneticists first engage pregnant patients and their supporters through structured conversa-

tions, usually in intake interviews. While many genetic counselors are well aware of the cultural barriers to communication posed by low-income, multilingual patients without advanced scientific vocabulary or training, we are often less aware of the cultural barriers we ourselves bring to the interaction. Counseling is always a cultural practice as well as a medical and a psychosocial one. Values such as "free choice," "health decision-making," and "the couple" as a unit are culturally specific, and they intertwine with the discourse of genetics. Counselors, no less than their patients, are culture bearers, and we bring multiple, sometimes contradictory resources and goals to our work in the health sciences.

Science has developed powerful tools to describe and analyze the body as a unified biologic object of investigation. While there is a range of recognized normality and abnormality, all human bodies are structurally and functionally similar. Down syndrome, for example, is *always* caused by an extra chromosome 21. Its causes, effects and consequences are therefore assumed to be consistent although the severity of the syndrome varies. Yet "real bodies" are culturally embedded. Recent immigrants from the Haitian countryside do not recognize Down syndrome. No word exists in Creole for the condition. The incidence of Down syndrome is invariant worldwide. But in a country with the highest infant mortality rate in the Western hemisphere, babies die from many causes, and Down syndrome may go unrecognized. Non-recognition of the label may also reflect other cultural and political experiences. Haitians living in New York City have already confronted alternative definitions of their children's vulnerabilities. As one Haitian Evangelist father told us, while firmly rejecting amniocentesis on his wife's behalf.

"What is this retarded? They always say that Haitian children are retarded in the public schools. But when we put them in the Haitian Academy (a community-based private school), they do just fine. I do not know what this retarded is."

In his experience, "chromosomes" seem a weak and abstract explanation for the problems a Haitian child may face. Among Chinese mandarin-speakers, no particular "syndrome" based on physical similarities among children with Down is perceived, but everyone responds to descriptions of mental retardation.

The language of science offers a powerful lexicon for labeling illness and disabilities, but it is not always useful to all populations. For example, in the small towns of San Luis, Baranquitas, and Limonetas outside of Maracaibo, Venezuela, where an international team of scientists is investigating highly inbred families at risk for Huntington disease, researchers had to relearn the definition of a pedigree. When the team would query, "who inherits this disease?", family members would always name huge cohorts of relatives. The common belief in this community is that anybody in a Huntington family

inherits the disease, but only certain people get sick. People in these towns have theories about what life-style changes might inhibit or delay the disease, and patients are cared for quite publicly (Wexler, personal communication). Risk has been culturally collectivized, and this may benefit the sick, who function in their families and communities longer than many North American counterparts. Will the introduction of individual screening change this collectivizing strategy of caring for the ill? Will the burdens of disease and caretaking become more private?

Some groups have a great deal of experience in coping not only with genetic conditions, but with genetic screening programs. Urban African-Americans, for example, bring not only a rich repertoire of community beliefs about sickle cell trait to interactions with genetic counselors, but also a collective historic memory. Current screening programs for the trait are greatly improved over those piloted in the early 1970s. However, the disorganization, lack of education and counseling and abusive uses of trait status information in employment, the military, and health services initially made many African-Americans suspicious of sickle cell screening programs [3-5].

While the profession of genetic counseling was developed to translate the language of science into usable and popular discourse for patients, that translation is not easy or obvious. The path to communication is fraught with obstacles, many of which begin as clients enter the counseling room. One early chasm in communications is apparent as counselor and client exchange greetings. Many counselors begin a session with some variant of the question, "What is your understanding of the reasons for this visit?", hoping to encourage an open-ended conversation in which the client's level of knowledge about prenatal diagnosis, hereditary conditions and family health history can be assessed quickly. Such a seemingly neutral question may, however, meet with a range of problematic answers. One white, highly educated husband (who turned out to be a biostatistician!) immediately answered, on "the couple's" behalf, that they had come for a decision-making tree in order to ascertain whether the pregnant wife needed amniocentesis, and what they were to do with the information, should the results be positive. His response effectively squelched any exploration of those counseling issues that could not be mathematically modelled. A Dominican low-income mother of three may respond, "*por culpa de mi edad*" (literally, "for the fault of my age") while rural African-American farming families may defer and remain silent out of respect for medical professionals. Families from India may interpret such a direct and leading question as impolite.

Effective intake interviewing requires that literal problems of translation be resolved. While some counselors are lucky enough to work with trusted genetic assistants, nurses or secretaries who understand and can translate their agenda very well, others must rely upon more informal translation services. It

is difficult for example, to work through an eight-year-old daughter, kept out of school to translate for her pregnant mother, for whom the meaning of "LMP" is still a mystery. It may be even more difficult to elicit accurate information through a husband, brother or male neighbor who finds himself deeply embarrassed to be inquiring about prior miscarriages and abortions. Supporters may also hold firm opinions about what the client should do, should she have "the needle test" and learn of an affected pregnancy. While most counselors are comfortable with treating "the couple" as a decision-making entity, they are probably less comfortable having to include the Chinese mother-in-law. Yet she may be the most influential figure in her daughter-in-law's pregnancy. While a Puerto Rican woman may say, "he says it's my business if I have that test or not," when queried about her mate's intentions, she may also be living under a threat of male abandonment if miscarriage or abortion follows her decision. In summary, the counselor's commitment to supporting an individual pregnant woman's decision-making must sometimes come up against a commitment to complex cultural relativism.

Even when problems of literal translation are solved or minimized, many other communicative barriers exist in counseling underserved groups. Statistical language constitutes one obvious barrier. Talking in numbers may work well with highly educated, information-seeking, medically compliant patients, but this strategy may be less useful to less privileged women. Low-income African-American women, for example, often express a sense of statistics based on personal experience that varies radically from the perspective of middle-class couples. When a woman has given birth to four other children, comes from a family of eight, and all her sisters and neighbors have had similar histories, she has seen scores of babies born without recognizable birth defects. It requires a leap of faith in abstract reasoning to contrast these experiences with a number produced by someone she has never met before, proclaiming that the risk of having a baby with a birth defect is steadily rising with each pregnancy. Among middle-class professional families, where child-bearing is likely to be delayed, we are often discussing a first, or at most a second pregnancy. To such couples, 1/300 sounds like a large and present risk, while for the low-income mother of four, the same number may appear very distant and small.

Moreover, low-income women lead lives which are often at risk in ways only barely imaginable to a middle-class genetic counselor unfamiliar with these non-genetic problems. How do we convey a 25% risk of sickle cell anemia when a low-income pregnant Afro-Puerto Rican woman experiences a 100% chance of running out of food stamps this month, a 25% risk of having one son or brother die in street violence, and an 80% chance of getting evicted by the end of the year? A one in 180 chance of having a child with a chromosome abnormality at age 35 is probably the best odds she is facing. What looms large for the counselor may seem quite small to the pregnant patient. The

extreme vulnerability of undocumented immigrants, or children with severe school problems are problems of *now*. The same cannot be said of risks to the unborn fetus. Thus, even with the best of intentions, priorities between counselors and patients may vary dramatically.

Poor people, especially recent immigrants, lead very complex lives. Their need for services to which they have little or no access may be profound. When a genetic counselor asks, "Do you have any questions for me?", a middle-class family is likely to respond, "What's the rate of risk if we undertake another pregnancy in two years?" But underserved, underprivileged patients are likely to ask, "Where's the medicaid office?"; "my husband's hitting me and I'm afraid it will hurt the baby, will it?"; or "I've got a terrible infection 'down there'." Middle-class families also have problems with their bills, with family violence and with sexually transmitted diseases. But they usually have both the financial resources and long-standing experiences with medical specialization that enable them to compartmentalize these problems.

In addition to issues of literal and metaphoric translation, professional language and medical specialization, there is another communicative barrier that counselors often encounter in meeting with women from underserved groups. Above all, the meaning of a particular condition is what is under negotiation when the subject of prenatal diagnosis and possible abortion is breached. All conditions have local, cultural as well as scientific meanings. Albinism, for example, has a genetic origin and a medical etiology, but it also has local meanings which cannot be found in medical texts. For many Puerto Rican families, whitening is part of *adalandarse* (tr: getting ahead) through upward social mobility. A very light child may be viewed as a blessing, given the realities of racial discrimination within their own communities, and in the larger society. For some African-American families, however, the same condition raises the stigmatizing question of nonpaternity; its diagnosis may powerfully increase tensions between a new mother, her partner and other relatives, until the condition is fully understood. Among many low-income Hispanic families, physical stigma, especially if very visible, present a more stressful problem than does mental retardation. Several families whose children had Down syndrome used the word "normal" over and over again to emphasize their relief that their children were growing well, and didn't look very different than other children in their communities. Mental retardation was the least of their concerns, at least with small children. In a rural African-American community where Coffin-Lowry syndrome has been studied in one large kindred, people remarked affectionately on family resemblances among affected boys. They consider their mentally retarded children to be the "easy" ones, when compared to the "normals," who confront severe problems in daily life. *Their* hierarchy of the severity of different medical problems may not be *ours*. We cannot assume that science provides a ready mode of interpretation of what to test, and when to terminate.

Many ethnically coherent communities guard pedigrees carefully. Where marriages are arranged, visible stigma represents a threat to the whole lineage and its successful reproduction within the community, not just to the individual. Family members often carry what sociologist Erving Goffman [6] labeled a "courtesy stigma."

Communities may also develop their own strategies for assessing and lowering genetic risks. The *Chevra Dor Yesurim* ("the Organization for the Generations") originated in a collaboration between the genetics department at Mount Sinai Medical Center in New York City and a Rabbi in the Hasidic Jewish community in Brooklyn. As the father of several children who had died of Tay-Sachs disease, this Rabbi fully understood the personal and ethical issues from the perspective of his community. Prenatal diagnosis and abortion of affected fetuses were culturally problematic. A program to screen potential partners prior to marriage made more cultural sense. The screening program he helped to develop now does more carrier testing than any other program in New York State and has networks in Canada, Israel and England. Screening is confidential, family-initiated and used to arrange marriages that will be "compatible." Since potential mates are screened before couples are even introduced, "incompatible" matches (ie, those in which both individuals are carriers) are never arranged. This eugenic solution to a culturally perceived problem has had enormous success in lowering the incidence of Tay-Sachs disease. Here, a "new reproductive technology" sustains an old, patriarchal tradition of community-arranged marriages. Indeed, seemingly "new", or "modern" arrangements may often be used by cultural communities to bolster their own agendas. Anecdotally, some genetic counselors who work with Hasidic families have noted that babies born with severe disabilities are frequently sent to live with relatives, preferably outside of New York City, or even the United States. The children are supported through Social Security Insurance payments sent abroad. A policy designed to allow families to better care for their disabled children at home protects the "secrecy" of the pedigree, allowing others in the family to successfully arrange marriages despite the stigma of caring for a disabled child.

Pregnant women and their supporters may have many reasons to reject "the needle test," or to continue a pregnancy despite a prenatal diagnosis of a condition considered quite serious among counselors. In some cases, a condition may be well understood, and not considered sufficiently problematic to merit abortion. For example, here is the voice of one amniocentesis refuser:

"I'm a foster mother, I got five foster children. Right now, one's mentally retarded. I know what that is. It's not what I want, but if it happens, I'll keep that baby. I made it, it's my responsibility, I wouldn't feel good about having an abortion. I know what it is, I'm not scared."

In other cases, the opposite effect may occur, where a diagnosed condition is so arcane that its ambiguous reality is hard to accept. In an interview following the birth of her baby who had been prenatally diagnosed with trisomy 9, a Haitian mother said that she might have aborted for Down syndrome, but the uncertainty regarding the exact nature of the rare condition found in her fetus was too unsettling. If *they* couldn't predict without equivocation just how her fetus would turn out, she reasoned, she might as well take her chances. This problem is multiplied in medically underserved families and communities where the methods of laboratory-based science are quite foreign. There *is* something "almost magical," or at least, incommensurate, in being given a diagnosis that may well spell death to the fetus based on reported sightings of invisible objects floating in three tablespoons of yellowish fluid. While genetic counselors and geneticists work hard using karyotypes and other visual aids, this breach is not always easily healed.

Moreover, some individuals and groups hold strong religious beliefs in which abortions have not only theologic but practical consequences. Many Hispanic women choose multiple early abortions to end unplanned pregnancies, but consider late abortion to be a mortal sin. This distinction is underlined linguistically: they will use the word *aborto* for early terminations, but describe a late pregnancy termination as *sacarme el niño* ("to have the child taken out of me"). Among many Evangelical Haitians, Dominicans and Puerto Ricans, there is a strong belief in miracles. Counselors and pregnant women invoke different bases of explanations. Statistics, after all, belong to the realm of mathematic prediction, while God's protection of a specific pregnancy is the reward for faith. Finely honed, female-centered folk theologies are at stake, and not some generalized notion of "Catholic" or "Protestant" dogma. We do not think that you can "predict" what a pregnant woman will do when confronted with the possibilities of prenatal testing on the basis of religion alone. Religious faiths are embedded in social practices: time spent in churches, judgment and supports of neighbors, friends and family members, and social services offered or discouraged through a denomination. Belief and religious practices are always local, no matter how attached they may also be to international Churches.

When confronted with such differences of interpretation, counselors often turn to their own culture, the culture of science, pulling out communicative resources that they hope will be helpful. Yet sometimes, these strategies inadvertently represent a bias. Many counselors will accept a "no" to the question, "do you wish to have amniocentesis?" from a 34-year-old pregnant woman without much probing, but may counsel a bit longer and neutralize with greater difficulty when the woman is 42, knowing the woman is at greater risk, and wishing the woman's perceptions matched their own.

Another form of subtle bias among health professionals is overcounseling, a strategy for cascading information over the head of a patient who seems non-compliant. Such an approach may alienate a patient or frighten her into submitting to a test she wished to refuse until excessive information overwhelmed her. For example, a very bright 18-year-old African-American who carries the trait for sickle cell anemia is sent for genetic counseling. She expresses concern about alcohol and crib death (there have been two in her family), but the genetic counselor wants to focus on sickle cell anemia and amniocentesis. Blood results for her partner become available, and he is negative. At first, everybody rejoices, but the counselor keeps speaking about what the test *can* reveal. By the end of the session, an 18 year old with no indications for amniocentesis is speaking as if she wanted the test.

Most subtly of all, counselors, like many middle-class Americans, may experience cultural differences as perplexing, or even threatening. They often employ what might be labeled psychological jargon to bridge a communication gap. When a 39-year-old pregnant Puerto Rican woman who is a charismatic Catholic refuses the test because "I praise the Lord who has given me this baby," a counselor may well say, "she's denying," "she's repressing," "she's too defensive to hear me," or "she's resisting," rather than acknowledging what she herself does not understand. Conversely, pregnant women may use the counselor's psychological vocabulary in non-psychological ways. One low-income Puerto Rican mother of three having a fourth baby at 40 said, "I've been depressed ever since I come up pregnant," and the genetic counselor rushed in to reassure her, "It's normal, you're older, it's depressing when you've got lots of family responsibilities." But the patient looked at her in disbelief: *she* meant that this pregnancy was "low-energy." She was not speaking of psychological depression: "My energy's been depressed, I'm happy to be havin' this baby."

When a counselor encounters a patient's response that she finds perplexing, the problem may be rooted in the different cultural resources which each is using to interpret health, illness, causality and pregnancy management. Such cultural responses are illustrated in the four case studies which follow.

CULTURAL CASE STUDIES

Case # 1:

Grace is a 26-year-old Chinese woman married to Jason, 27 years old. Together, they have one child. Jason has three children from a previous union. Grace has lived in the United States for 12 years; her English is halting. Jason's English is quite good. Although an interpreter was offered, Jason wanted to do his own translating. The couple live with Jason's parents in

Chinatown, where most of their immediate family also live. Grace receives regular prenatal care in Chinatown, and Jason's employer provides complete medical insurance.

The couple was referred for genetic counseling because their son was born with cleft lip and cleft palate. Grace is currently 16 weeks pregnant. They are concerned about the risk of recurrence. The couple appeared extremely subdued, asked few questions, and expressed no visible affect, even when discussing what were clearly emotionally charged issues for them. The husband translated his wife's sense of guilt: she believes the son's birth defect was caused by her use of sewing scissors during the first pregnancy. When queried directly, Grace seemed to doubt the association, but in view of the unknown etiology of her son's condition, she could only question whether her use of the scissors had indeed played a role. Her guilt concerning her own role in the child's birth defect was strengthened by the existence of three healthy children from Jason's previous union.

Grace wanted a guarantee that this fetus would not be affected, as much for Jason's parents as for herself. She expressed guilt at having brought shame to the family. Prior to corrective surgery, the son's disability had been hidden by surgical tape whenever he was taken outside. This shame was also the reason Jason refused a translator: they were reluctant to have outsiders know about the birth defect.

During the counseling session, multifactorial inheritance was discussed, and the couple was given a 2–4% risk of recurrence. Both seemed to understand the information quite well, and Grace remarked that the number was much less than what she had feared. In addition to expressing her relief, Grace told us that she would still refrain from using scissors throughout this pregnancy.

This case illustrates:

- 1) There is fear and mistrust of speaking with "outsiders" about a shameful family matter. This is especially true about using an interpreter, who could be connected to the Chinatown community.
- 2) While the minimal affect displayed by the couple could easily be interpreted as denial or failure to cope in Western psychological terms, it helps to know that calmness in the face of adversity is a highly esteemed quality in Chinese culture. The couple's behavior from a Chinese perspective is admirably appropriate.
- 3) Although the couple sought help from Western biomedical professionals, they did not relinquish their beliefs in Chinese forms of explanation. The two systems of belief and practice coexist.

Case #2:

Latasha, an African-American woman of 35 was referred for genetic counseling in her third pregnancy. Her family history seemed unremarkable.

She had a 15-year-old son, and a 10-year-old daughter, both in good health. She denied any family health problems, including mental retardation. She joked about having a "wild" sister as her only health problem. After counseling, Latasha chose to have an amniocentesis, which she reported was her doctor's strong recommendation.

When Latasha arrived for her amniocentesis, she was accompanied by her 15-year-old son, Jackson. He had coarse facial features, a bulbous nose, large ears and widely spaced teeth. He also had scoliosis and extremely garbled speech. When asked how her son was doing in school, she said the school was "pleased with his progress." When the counselor asked whether Jackson went to a special school, she said, "the bus picks him *and his cousins* up every morning." After the amniocentesis, another pedigree was taken which revealed that she had two sisters with children like her son Jackson. Her "wild" sister was the only one without children like Jackson. Latasha also had a brother like Jackson.

Medical records revealed that Jackson and his cousins and uncle all had Coffin-Lowry syndrome, an X-linked disease associated with mental retardation, coarse facial features, short stature and distinctive hands and fingers.

Latasha was again counseled regarding X-linked inheritance of Coffin-Lowry syndrome, and the amniocentesis revealed a male fetus. After all the options were presented to her, Latasha said that she would discuss them with her mother. The next day, she called and said that her mother was furious about all "this new fangled scientific nonsense." She had prayed to the good Lord who had come to her in a dream stating that they were considering an abominable option. Latasha's mother also said that Jackson and her other grandchildren like him were "much better off" and less troublesome than the "wild ones." They went to special schools and had good care. It was the normal children, exposed to drugs, one a runaway, one having done time in prison, who worried her. Latasha's boyfriend was also "proud as a peacock" to be having a boy, and Latasha worried that he would abuse her if she chose an abortion. She also said that she might have considered abortion had the tests been more definitive, but she could not end the pregnancy on the basis of a 50-50 chance of the fetus being affected.

A detailed pedigree revealed five boys with Coffin-Lowry syndrome, and seven carriers. The family agreed to allow linkage analysis, and a genetics team visited with them. The family lived in severe rural poverty. Family life centered around Maud, the grandmother, who only gave permission for the linkage study after discussing it with her Baptist minister. The affected boys were viewed as look-alike cousins. Several home visits helped us to understand the following points:

- 1) Mental retardation is not a severe problem in this family, where affected boys are viewed as contented, easily cared for and well served by special

state schools. The normal children are considered more “at risk,” for they live in an environment fraught with drugs, petty crime, and other extremely worrisome conditions.

- 2) Religious beliefs, practices, and networks of support actively figure in daily life and decisions surrounding health care.
- 3) This is a matrifocal family. The locus of familial decision-making rests with the women. While men may be said to have a “veto” over health decisions based on their power of disapproval or even threats of violence, daily life is organized through women’s helping networks.

Case #3:

Migdalia, a 16-year-old Hispanic pregnant woman, was referred for genetic counseling because of a family history of spina bifida. She was 16 weeks pregnant, and this was her first pregnancy. Her boyfriend Carlos was 19 years old.

Migdalia came to the counseling session herself, expressing great concern about spina bifida. Her younger sister has the condition, uses a wheelchair, is incontinent and blind. She travels by bus to a special school. Migdalia and her mother are both devout Catholics. Neither approves of abortion. But Migdalia’s mother wanted her to have the test, and to abort if the fetus was going to have spina bifida. “It’s a cross to bear, God gave it to her, in my mother’s life, and she don’t want it for me, too.” Migdalia feels that her parent’s separation was deeply influenced by the “suffering” (her word) her sister brought to their mother. “We love my sister, it’s just very hard.”

Two weeks after the counseling session, Migdalia had an amniocentesis. It revealed no neural tube defects, but the fetal chromosomes were 47,XXY. Migdalia, her boyfriend Carlos and her mother all met with the genetic counselor, and the implications of Klinefelter syndrome were explained to them, including sterility and the risks of learning disabilities and mental retardation. “I was only concerned if my baby could walk and see, this other stuff didn’t concern me. They said he’d be normal, he might be slow-minded, but that’s ok, as long as he looks normal, I’ll be there for him.” Both Carlos and her mother agreed that the health of the fetus was “in the hands of God,” and that she should keep the pregnancy.

Three years later, Migdalia came back, self-referred, for an amniocentesis in her second pregnancy. She and Carlos were having a second baby. Again, she wanted reassurance that the fetus would not have spina bifida, “If my first kid was having what my sister’s got, I’d need a lot of help. But he’s growin’ up normal, he looks ok, he acts ok, he’s a really nice kid. I could never abort for *that*, he’s developing each day, I can handle this, as long as the baby looks normal.” A second amniocentesis revealed a diagnosis of 46,XX. When asked how she felt about having known about the Klinefelter diagnosis in her first

pregnancy, Migdalia said, "It's a good thing, I wasn't too scared for the rest of the pregnancy, I was relieved it wouldn't be like my sister, and I just worried about whether he'd be premature. It's better to know in advance, to check it all out. My son has a little problem, not a big problem, and I'll be there for him when it's the right time to explain it."

This case illustrates:

- 1) Prior experiences play a large role in how birth defects are perceived and how pregnancy decisions are made. Spina bifida looms large in Migdalia's experience. Prematurity, an affliction of low-income young mothers, is also a concern for her.
- 2) Religious practices are highly influential, but not deterministic. Religious language is intermeshed with concrete descriptions of the mother's problems as the primary caretaker for a disabled child. Both Migdalia and her mother would have supported an abortion decision if the fetus had a neural tube defect.
- 3) For this family, as for many other low-income Hispanic families, "physical stigmata" are considered extremely serious. Less visible problems, like learning disabilities, or sterility, are not seen as severe.

Case #4:

Louise and Bob, both Anglo-Protestants, came for genetic counseling when Louise was nine weeks pregnant. She was 40 and an urban planner; he was 48 and a biostatistician. This was their second pregnancy. Their first son was five years old. Bob took notes during the counseling session, engaging the counselor in a technical discussion of the risk figures for CVS vs amniocentesis before the couple came to a decision. He wanted a comparison of the accuracy, sensitivities and specificities of each procedure. He even constructed a decision-making tree, and remarked that he would love to write an article on this fascinating informational problem. Louise eventually had an amniocentesis at 15 weeks.

Two weeks later, chromosome results revealed trisomy 21. Louise immediately terminated the pregnancy. Although both partners quickly resumed their careers, Louise had a very difficult time with the aftermath of the decision. She called to ask for a support group, and followed up with several additional counseling sessions. Among her problems were the need to know "what caused this accident of meiosis," fear of the judgment of colleagues and fear of her mother, who had expressed strong antiabortion sentiments. Louise had no one with whom to share her feelings, and her husband, while supportive, was rarely at home. A seemingly rational, statistically based decision-making process had left Louise socially and culturally unprepared for its isolating consequences.

This case study suggests:

- 1) Scientific language is shared by sectors of the middle class for whom it also provides a belief system. This language may mask as much as it reveals, leaving the woman who terminates an affected pregnancy unprepared for those aspects of her experience not easily expressed in the discourse of scientific decision-making.
- 2) Professional couples often lead busy lives which leave them relatively isolated from supportive kin and community. Colleagues and kin do not figure large in this case study. Support is more easily sought through paid, professional services.
- 3) The cultural values of a white, professional Protestant couple at first seemed unremarkable since they were compliant, highly rational clients. It was only Louise's pained and isolated reaction to her decision to terminate that allowed those of us from similar backgrounds to really "see" the sociocultural aspects of this case.

In all of these cases, "talking genetics" involves engaging the cultures, languages, assumptions and values embedded in each community. This is as true for the Chinese-speaking daughter-in-law as it is for the wife of the biostatistician; as important for the matrifocal kinship network that values the steady temperament of its mentally retarded sons as it is for the Puerto Rican teenager who would abort for spina bifida, but not for Klinefelter syndrome.

We are not suggesting that "cultural difference" is a convenient catch-all that can substitute for psychological evaluation or terminology. All counselors know the immense range of individual variation in prenatal diagnostic decision-making, and the profound influence of prior family and reproductive history on acceptance or rejection of amniocentesis and/or abortion. Recognition of the moments of cultural noncommunication or miscommunication is an achievement that may open doors rather than close them.

TOWARD CROSS-CULTURAL SENSITIVITY IN GENETIC COUNSELING

These nine suggestions are intended to improve cross-cultural fluency:

- 1) We need to learn to listen carefully to our own cultural responses. Genetic counselors are trained to be highly sensitive to the psychological resources and problems of their patients, but we are unlikely to receive comparable training in the cultural resources and problems patients also bring to a counseling situation. Counselors trained in population genetics understand that particular ethnic groups transmit specific diseases, but we may not necessarily see the analogous transmission of specific ways to interpret illness and health in pregnancy, child-rearing and family life. To the best of our knowledge, none of the existing genetic counseling/nurse genetics training programs offers course work in cross-

cultural counseling. Such courses would be helpful in orienting new counselors to the complexity of working in urban medical centers, and in helping us all to recognize our own cultural biases as well as those of our patients.

Introducing this kind of course work will not solve all the problems described here, many of which must be attributed to socioeconomic inequalities. As individuals, we can do very little to alleviate these problems. But as a profession, we need to lobby to keep abortion safe, legal and funded, and expand genetic services, especially to provide special programs to reach underserved populations.

- 2) Contact a medical or urban anthropologist at a local college or university. She or he may be able to provide bibliography, consulting or general insight into the ethnic communities in your area.
- 3) Consider taking a course in cross-cultural health issues or a family therapy course that focuses on cultural variation.
- 4) Participate in journal clubs and genetic counseling roundtables. Consider devoting some sessions to articles on local cultural groups.
- 5) Invite related professionals to selected case reviews. For example, a family therapist, medical social worker, psychologist or medical anthropologist who has worked with the patient's cultural group might provide helpful insights.
- 6) Contact people with special expertise in the cultural communities you need to understand better. Public health nurses, social workers, outreach workers and community service workers may all be "gate keepers" who are willing to help.
- 7) Read and use the articles in the path-breaking volume on cross-cultural genetic counseling edited by Biesecker, Magyari and Paul [7]. Especially useful therein [7] is the check list provided in "Practical Methods in Reaching and Counseling the New American" by Lum and Whipperman, pp 188–205. Their suggestions range from the delicious (eat in ethnic restaurants) to the intense (learn Chinese) to the immense (join and work in a local ethnic institution, like La Raza Health Network). The checklist emphasizes an important point: it's not the completed task but the spirit of open learning that really counts. Learning about local cultures can be immensely interesting: poetry, plays, films and novels often portray cultural experiences and dilemmas quite vividly.
- 8) Submit relevant case studies with a bibliography to *Perspectives in Genetic Counseling*.
- 9) Apply for funding geared to outreach. Information on available funding may be found in your state health department, genetic services division, and in the Federal Office of Maternal and Child Health which is establishing a network of Special Projects of Regional and National

Significance. Some of the SPRANS grants projects that have been aimed at overcoming ethnocultural barriers in genetic services are described in conference proceedings forthcoming in the *American Journal of Medical Genetics*. Collectively, these projects are an immense inspiration; they are also fragile, for they depend on sources of funding that are only temporarily available.

There are innovative programs scattered across the USA that address outreach of genetic services to diverse cultural minorities. These programs have developed expertise in recruiting and training bilingual/bicultural genetic assistants, running ethnocultural workshops and conferences to educate healthcare providers, produced or translated culturally relevant written, video, and graphic materials, formed advisory committees to oversee outreach efforts that include ethnic community leaders and consumers, developed community outreach educational events in locales ranging from churches to labor unions, from health fairs to school libraries, developed and disseminated culturally relevant, linguistically appropriate prenatal risk questionnaires, and implemented satellite genetic clinics in places that community members find comfortable. From their work, we have learned a great deal about how to include key family members and special friends into genetic counseling sessions, how to accept radical differences in perceptions of risk and causality of illness and health, how to hook into existing community resources to create a culturally sensitive counseling environment, and how to acknowledge the impact that culture has on the utilization of genetic services and decision-making.

Genetic counselors, like all Americans, live in a world increasingly defined by multicultural diversity. We need to abandon metaphors of the melting pot in favor of images of a stew or gumbo characterized by a rich and flavorful lumpiness. The challenge we now face is to develop and deliver culturally relevant, respectful and useful genetic services in an America in which diversity is a permanent aspect of the social landscape.

ACKNOWLEDGMENT

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Understanding Our Infertile Genetic Counseling Patients

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INTRODUCTION

This workshop aimed to identify and discuss psychosocial aspects of the infertile couple seeking genetic counseling and the genetic counseling patient with a prior history of infertility. The persistent legacy of infertility can and does influence decisions, life choices, parenting and definition of self [1].

Infertility is believed to affect 15% of all couples seeking pregnancy [1]. Infertility is generally defined as the inability to conceive after one year of planned intercourse. Included in this group are those couples who are able to conceive, but repeatedly experience pregnancy loss. Of couples who obtain proper medical evaluation and treatment, 50% will respond to treatment. In contrast, only 5% of infertile couples who do not seek medical intervention will subsequently conceive [2].

Each couple faces unique consequences of their infertility, depending on the contributing conditions and the solutions they find as they confront their inability to give birth to a child. Infertility is a bio-psycho-social condition. As such, it presents challenges to the professional working with the infertile couple. Primarily, it necessitates the acknowledgment of the intrusiveness of the infertility experience into many areas of the individual's life including medical, psychologic and social relationships [1].

Case 1

Lori and Richard were referred to the genetics clinic by a local obstetrician following Lori's fourth first-trimester pregnancy loss. At the time of the initial appointment, Lori and Richard were in their mid-twenties. They were married at 19 years of age and worked together in a family-owned book bindery, and lived in a trailer on the "family farm." The counseling session reviewed the possible etiologies of pregnancy loss and the specific role of chromosome analysis in identifying chromosomal translocation. The couple refused chromosome testing because they felt their pregnancy losses were not so unusual since Lori's mother had seven spontaneous abortions. Lori confidently stated, "My mother had seven and then I was born!" The session concluded with my acknowledging their optimism based on the family history but again stressed the possible implication of a familial chromosome translocation.

Several months passed and a call was received from Lori reporting symptoms of an impending miscarriage. At that time, Lori agreed to chromosome analysis of the products of conception, which revealed an unbalanced translocation, 47,XX,+13q.

Karyotyping of the couple identified Lori as a translocation carrier, 46,XXt(8;13). Genetic counseling regarding risks for future miscarriage or the birth of a child with an unbalanced chromosome constitution was provided. Lori and Richard remained optimistic that they would achieve a live birth since such a pattern already existed in the family. They repeatedly used statements that minimized their risk during the counseling sessions. In the following year, Lori experienced two additional miscarriages, each with normal karyotypes.

A follow-up counseling session with this couple found them frustrated with the normal chromosome analysis of the last two miscarriages. They experienced increasing doubt about the role of chromosome translocation in their pregnancy losses. In consultation with their obstetrician, a limited infertility work-up was initiated. Temperature graphs and an endometrial biopsy revealed a possible luteal phase defect. A luteal phase defect is caused by an inadequate corpus luteum resulting in a deficiency of progesterone. Hormonal treatment was indicated.

The eighth pregnancy was conceived and supported with progesterone suppositories. At 13 weeks of pregnancy, Lori and Richard returned to discuss prenatal diagnosis. Lori was expressing optimism since her mother's eighth pregnancy had been successful. Richard was more openly anxious and carefully asked about the range of abnormalities that could occur in a child with an unbalanced translocation. Lori frequently turned to him and attempted to reassure him with statements like "it makes sense that all unbalanced would end in a miscarriage; it already happened to us" and "that's what miscarriages are for." Lori's statements appeared to be an attempt to reassure herself since she was visibly disturbed about the risks of miscarriage from prenatal testing. The session concluded with an agreement to pursue amniocentesis.

Amniocentesis was scheduled at 16 weeks and revealed an unbalanced translocation: 47,XX,+der(13),t(8;13)(p11;q11) mat. In the genetic counseling session, Lori repeatedly stated, "It wasn't supposed to happen like this; the eighth was going to be okay." Lori and Richard spoke of their concern that this might be their only chance at a full-term delivery. After a lengthy discussion, they decided to terminate the pregnancy at 19 weeks.

Lori and Richard attended a perinatal loss group and periodically met with the counselor over several months. Today, Richard and Lori have a daughter who was conceived with the use of Clomid and progesterone. Prenatal testing in this case revealed a normal female chromosome constitution, 46,XX.

Questions:

- 1) Can we assume that all untested pregnancy losses were chromosomally abnormal?
- 2) What was the impact of elective termination following abnormal results?

Case 2

A 31-year-old woman, Ann, sought chromosome testing for her newborn son, Ben. Ann had been in treatment for infertility for seven years. Her successful pregnancy resulted from ovarian stimulation with Pergonal (menotropin). Ann has been insulin-dependent since 17 years of age. Her infertility evaluation and treatment took her to three different physicians; she had several surgical procedures and many months of hormonal therapy. Her final treatment involved careful monitoring of her insulin and use of Pergonal by a reproductive endocrinologist. This monthly process of Pergonal and its associated blood and sonogram monitoring cost approximately \$2,000 to \$2,300 per cycle. In the 11th month of Pergonal use, Ann experienced ovarian hyperstimulation. Hyperstimulation results from sudden ovarian enlargement with increasing accumulation of fluid in the abdominal cavity and sometimes in the lungs. This often life-threatening complication is the major concern with the use of ovarian-stimulating medications like Pergonal.

For Ann, her hyperstimulation occurred concurrently with a conception. This very complicated medical condition found Ann hospitalized for nine weeks requiring ICU care for some of that time. At 39 weeks, Ann delivered by C-section a “normal” male with Apgars of 9 and 10.

At Ben’s first pediatric visit, Ann explained to the pediatrician that she was concerned that the hyperstimulation due to the use of Pergonal and the resulting hospitalization might result in developmental risks to her son.

Question:

- 1) Will genetic information/reassurance be enough for this patient?

Psychosocial Characteristics of the Infertile Couple

- A. Stoic
- B. Their identities as infertile people often have eclipsed other areas of accomplishment.
- C. Damaged self-image
Infertile patients may feel inadequate and defective. They may fear that God has judged them unworthy of being parents.
- D. Social isolation
Many infertile couples have withdrawn from relationships with adults who have young children. They feel out of step with their peers who are

preoccupied with pregnancy and childrearing issues. They feel misunderstood by friends and family. They often feel guilty about their negative feelings toward pregnant women and infants.

E. Sense of urgency

Time is passing them by; every month counts; frustration with waiting for procedures and test results (especially as a fetus matures).

F. Loss of control

1. scheduling of infertility procedures is disruptive;
2. medical expenses can be prohibitive;
3. scheduled sex—no spontaneity;
4. loss of control issues are especially difficult for achievement-oriented patients who are accustomed to setting and meeting goals and unaccustomed to failure.

G. Fearful and tense

1. due to having no diagnosis . . . being in limbo and continuing the search for elusive answers as time marches on;
2. due to a problematic diagnosis and the decisions that must be reached;
3. that the procedure could induce a miscarriage (especially in someone with a history of pregnancy loss); the need to know is balanced against fear of threat to the fetus;
4. if pregnant, there is an unwillingness to rejoice in the pregnancy and to bond with the fetus, especially if there have been earlier pregnancy losses.

H. Ambivalent about genetic counseling/prenatal diagnosis

1. reminder of possible defectiveness;
2. "just one more" in a series of tests that involves apprehensive waiting;

I. Hopeful of an answer that enables the couple to progress with plans for a healthy pregnancy.

J. Medically experienced

1. power issues may make people feel intimidated;
2. anger with professionals who still haven't helped them achieve a healthy pregnancy;
3. resentment generated by the need to be:
 - a. dependent upon professionals,
 - b. subjected to tests,
 - c. eternally waiting for results.
4. past relationships with other medical professionals may influence an individual's approach to the relationship with the counselor.

K. May be in some stage of mourning process

1. what is being mourned?
 - Loss of hope for a birthchild; loss of feeling of bodily wellbeing; loss of some dimensions in the marital relationship; loss of control.

2. denial that there really could be a genetic component to their problem (“I’m just here because my doctor thought I should come.”).
3. anger
 - a. at being subjected to one more procedure that may make the individual feel defective and unworthy of being a birthparent;
 - b. that efforts to have a baby are so torturous for them and so easy for others.
 - c. at being out of control
 - 1) bodily betrayal,
 - 2) wanting/not wanting definitive answers,
 - 3) facing the possibilities that there are no medical treatments for a diagnosed problem,
 - 4) at prospect of diagnosis, which may confirm feelings of defectiveness.
4. bargaining
 - a. if our results are okay, then I resolve to. . .
 - 1) stop smoking,
 - 2) stop drinking,
 - 3) lose weight,
 - 4) eat more nutritiously.
5. grief
 - a. at depriving self and partner of a birthchild;
 - b. at seeing one’s partner devastated by infertility, especially if that partner is the source of the couple’s infertility;
 - c. anticipatory mourning at the prospect of never having a birthchild.

What the Genetic Counselor Can Do?

- A. Recognize the couple’s anxiety and acknowledge their right to be anxious.
- B. Acknowledge one’s own conflict (not enough time to work through the emotions).
 1. painful emotions cause pain in oneself;
 2. if couple doesn’t offer information about their emotional response to being there, then they do not want to deal with it (in fact, the counselor should probe gently in order to assess what the couple would perceive as most supportive).
- C. Offer concrete information (first find out what they know already!)
 1. draw charts and diagrams they can take with them;
 2. write down statistical and other information;
 3. provide pertinent literature;
 4. encourage questions and further telephone contact;
 5. tell them how (and approximately when) they will be informed about test results;

6. ask whether they want to discuss now the options that will exist should results confirm a genetic problem.
- D. Facilitate open communication
1. encourage couple to talk directly to one another, rather than through the counselor or one partner expressing sentiments on behalf of the other;
 2. encourage "I need" statements;
 3. encourage positive feedback between partners when they meet one another's needs.
- E. Encourage empowerment through informed decision-making
1. how able are they to
 - a. take risks;
 - b. tolerate uncertainty;
 - c. raise a child with special needs;
 - d. develop and maintain support networks.
 2. can they gain access to others who have made similar decisions?
 3. who else will be affected by the decision that they make? What is the anticipated impact of the opinions of significant others?
- F. Make referrals
1. to other professionals who can help the couple process their feelings about the decision and to anticipate next steps in their efforts to have children.
 2. to any appropriate support groups.
 3. encourage the couple to reach out to their existing support network.

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Workshop: Countertransference and the Genetic Counselor

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Countertransference was first defined by Freud as the therapist's unconscious reaction to the patient's transference—the patient's unconscious displacement onto the therapist of patterns of behavior learned during childhood. Others use a broader definition in which countertransference refers to the therapist's conscious as well as unconscious reactions to the patient, as well as to the patient's transference. The therapist's past experiences and relationships lead to feelings that may interfere with optimal interaction with specific types of clients. While Freud recommends that the therapist overcome the countertransference, others suggest that recognition of transference and countertransference can assist the therapeutic process.

The purpose of this workshop was to explore the application of the concepts of transference and countertransference to the practice of genetic counseling. Issues addressed included: Do genetic counselors and their patients experience transference and countertransference? If countertransference occurs, how can genetic counselors develop skills to help effectively counsel in spite of it? What options are available for resolving personal conflicts related to countertransference? Do genetic counselors have problems related to countertransference that are unique to this profession?

A panel was convened whose members had recognized the influence of countertransference issues at some point in their professional practices. Karen Greendale discussed attributes of cases that became troublesome while she was coping with infertility. For example, she had considerable difficulty remaining neutral with couples considering termination of pregnancy because of relatively less severe birth defects or genetic diseases. She asked other genetic counselors at her Center to counsel patients considering prenatal diagnosis for sex selection. She had difficulty being tolerant of patients who were very anxious about problems that would likely resolve. Although she was able to hide these feelings in the interest of professionalism, she described her fatigue at the end of the day from constantly having to suppress them. At one

point she considered leaving the field because of the emotional strain of spending day after day working with pregnant women. Adoption of her daughter helped her to overcome these countertransference issues.

Lorna Phelps, a genetic counselor with Turner syndrome, said that she often discloses her diagnosis to other similarly affected women, and to parents of young patients, but rarely to patients with other diagnoses. Some genetic counseling issues were difficult for her to handle because of her own experiences. She acknowledged that it would be difficult for her to present unbiased information to a couple considering termination following prenatal diagnosis of Turner syndrome. Parents of a child with Turner syndrome are told in advance so that they have the option of meeting with another genetic counselor if they are uncomfortable. Ms. Phelps noted that every counselor brings experiences to genetic counseling that can positively or negatively impact upon the session, and that awareness of these issues can help each of us to be a better counselor.

Nancy Callanan spoke about genetic counseling during a pregnancy. Her comments were based on her own experiences, those of several colleagues, and a review of the available literature. Self-absorption, ambivalence and anxiety characterize the early stages of pregnancy and can lead to countertransference reactions. As the counselor advances in pregnancy, loss of privacy becomes a central issue. The genetic counselor must guard against over-identification and loss of objectivity with patients considering various prenatal diagnostic tests. We also need to consider the potential for transference and countertransference when a client who has experienced multiple miscarriages or the birth of an abnormal child is counseled by a visibly pregnant counselor. Strategies that might help pregnant genetic counselors cope were discussed. Ms. Callanan suggested that colleagues review the literature on psychologic and physical adjustments that occur during pregnancy to help them anticipate conflicts. Participation in peer support activities was also advocated.

Robert Resta represented parenting genetic counselors. He at some point decided to let patients know that he is a father and displays his children's photographs and artwork in his office. Many patients now ask whether his wife chose to have an amniocentesis; Mr. Resta discussed the pros and cons of answering this question. He concluded that being a parent has made it more difficult to counsel cases he had previously found troublesome, such as those involving sex selection or substance abuse during pregnancy.

Following the panelists' presentations, audience participation was encouraged. Many genetic counselors shared experiences that they could now recognize as examples of transference/countertransference. Suggestions for coping with patients who elicited such reactions were made. Some felt that, in general, the counselor should avoid situations likely to elicit countertransfer-

ence; others thought that working through such issues might in fact enlighten and empower the health professional. Sharing with colleagues at case conferences and in other arenas can help the genetic counselor to recognize which issues are likely to cause problems and to plan counseling strategies.

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Perinatal Bereavement Counseling In Genetics

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INTRODUCTION

In the United States, it has been estimated that approximately one million pregnancies end in miscarriage, stillbirth or neonatal death each year [1]. A fraction of other wanted pregnancies end in genetic termination and another 2–3% result in the birth of a child with a birth defect or genetic problem. Many families experiencing an unexpected pregnancy outcome have contact with the genetics team along the way. For some it is for prenatal diagnosis counseling; for others it is at the point of loss or following the autopsy at a grief conference. In each instance, it is essential for the genetic counselor to be both technically competent and knowledgeable about the relevant psychosocial issues. Versatility in applying the tools of grief counseling can enormously enhance both patient care and the counselor's level of comfort.

This workshop targeted counselors who wish to expand their expertise in the area of perinatal bereavement counseling. A theoretic framework is presented, along with questions, strategies and resources.

SETTING THE STAGE: BUILDING ON THE COMMONALITY OF GRIEF AND LOSS BETWEEN PATIENT AND GENETIC COUNSELOR

No speaker, authority, expert or other individual can provide the totality of tools necessary to enable the genetic counselor to provide the "perfect intervention" when caring for bereaved families. Knowledge, advice, and suggestions, when coupled with professional and personal experience comprise a large part of what each counselor will bring to the situation. The remainder comes from continually developing skills and broadening one's repertoire of experience with patients in crisis. This generally follows as a natural out-

growth of a willingness to take risks and reach out to other human beings who are emotionally in pain.

Bereaved families are needy. They are experiencing pain and confusion. They often are confronted with many difficult decisions as well. While each family and caregiver brings many unique elements to their relationship, there are some commonalities about grief that supersede the specific type of loss. The feelings during and following loss, the needs and issues faced, are much the same, even if the loss is shattered hope or the death of a dream. Families experiencing a perinatal loss, whether it is the unexpected end of a pregnancy or the decision-making that occurs following abnormal prenatal diagnosis, all have begun to travel down the common road of pregnancy. The psychologic milestones along this road are known as the developmental tasks of pregnancy; with dream-building being just one of these tasks. A good understanding of this adaptive process is essential for providing appropriate support and intervention.

Adaptation to Pregnancy

In the conference keynote address by Marfatia, Punaless-Morejon and Rapp [2] regarding the provision of genetic services to underserved populations, one predominant theme was the importance of acknowledging patients' cultural customs, values and beliefs. At few times in the life cycle is this as important as it is in dealing with issues related to childbearing. Pregnancy and parenthood take on different meanings for various individuals and families, as well as for entire cultures. Understanding these issues is an important aspect of providing appropriate counseling. Regardless of our acknowledged differences, families and especially the parents who have experienced a childbearing loss have all shared the common experience of pregnancy. In fact, there are recognized developmental tasks of pregnancy that are the psychologic milestones along the road to parenthood. An outline of these tasks by trimester follows in Table 1. The emphasis on the psychologic adaptation of mothers is due to the research concentration on women rather than men and families.

In light of the huge amount of psychological work that occurs during pregnancy, it is of no surprise that pregnancy is regarded as a developmental crisis [4]. It is a turning point between phases of the life cycle in which emotionally charged tasks must be completed and there is no turning back to a former psychologic state. Developmental crises are marked by periods of emotional disequilibrium which, under favorable conditions, resolve as specific maturational steps are completed, leading to new goals and functions.

Although differences in the maternal and paternal adaptations to pregnancy are evident in Table 1, two other observations may also contribute to the differences in the way mothers and fathers react to reproductive losses. For the mother, the loss always involves a physical loss, a loss of a part of herself. For

TABLE 1. Psychologic Tasks of Pregnancy*

-
- I. The First Trimester
 - A. Suspicion and confirmation of pregnancy.
 - B. Resolving initial ambivalence about pregnancy.
 - 1. "Who me?" "Not now!"
 - 2. Importance of factors contributing to the decision to become pregnant
 - C. Acceptance of pregnancy; fetus viewed as part of mother's body.
 - 1. Mastery for mother evidenced by: "I am pregnant."
 - 2. Mastery for father evidenced by: "She is pregnant and I am the father."
 - D. Relationship issues begin to emerge between prospective parents.
 - E. Prospective parents begin to:
 - 1. Relive own childhoods.
 - 2. Free themselves of conflicts from own childhoods.
 - 3. Rework relationships with own parents (especially mother).
 - F. Mother's somatic changes lead to feelings about body image and sexuality.
 - II. The Second Trimester
 - A. Realization of fetus as separate individual.
 - 1. Mastery by mother evidenced by: "I am going to have a baby."
 - 2. Mastery by father evidenced by: "We are going to have a baby."
 - B. Bonding facilitated by:
 - 1. Quickening.
 - 2. Fetal heartbeat.
 - 3. Sonography.
 - 4. Amniocentesis/prenatal diagnosis results.
 - C. Begin to fantasize about idealized child.
 - D. Seek out and turn to role models.
 - E. Changes in own relationship to partner continue.
 - F. Unresolved conflicts with own parents may continue to resurface.
 - G. Physical changes in mother lead to issues regarding sexuality and body image.
 - III. Third Trimester
 - A. Baby viewed as separate individual; ready to live outside mother.
 - B. Fantasies about the idealized child continue.
 - C. Taking on of parenting roles; "nesting."
 - D. Preparation for birth; labor and delivery.
 - 1. Mastery by mother evidenced by: "I am going to become a mother."
 - 2. Mastery by father evidenced by: "I know my role in the birth process, and I am going to become a father."
 - E. Mother experiences physical discomfort; is anxious to give birth.
 - F. Mother acknowledges fears about labor and delivery.
 - IV. After Birth
 - A. Parent-infant bonding intensifies.
 - B. Reconciliation of fantasies for idealized child.
 - C. Ongoing adaptation to roles as parents.
-

*Table 1 is adapted from material in Reference 3.

the father, the loss is conceptual. When asked during pregnancy about their fantasies for this child, mothers describe parenting a newborn, often together with the father. Fathers, however, dream about playing with an older child. Hence it is important to establish each parent's perceived loss.

Loss of the Perfect Pregnancy

Examples of reproductive losses range from miscarriage, stillbirth or early infant death to such situations as wanting a boy and having a girl, or even enduring a long uncontrolled labor that may also require unexpected medication. A less than perfect child, a mother and her baby being separated so the baby can be monitored, the grief after abortion or placing a baby for adoption, or any other deviation from the planned dream or fantasy all represent childbearing losses. Though some of these experiences may seem to be more painful than others, the thing to remember is that no one else really knows how invested and devastated someone is. A cesarean birth or a miscarriage could be the most tragic and overwhelming experience to one woman and a minor event to another. The ultimate challenge is to meet people where they are and to support them if they need it, no matter how each of us thinks we would handle the situation in our own personal lives.

During the last decade, especially among industrialized nations, pregnancy has become an increasingly high-tech experience. As reproductive technologies from infertility treatment to antenatal diagnosis and care for the high-risk newborn increase in utilization and acceptance, so do parental expectations for a healthy baby at the end of the pregnancy. This increase in parental awareness and expectations is partially a consequence of the vast amount of media attention devoted to these technological advances.

Just as the increase in technology has promoted healthy pregnancy outcomes, it has concomitantly raised new issues regarding attachment, loss and adaptation in pregnancy. Table 2, which specifically pertains to the experience of amniocentesis, illustrates how loss and attachment issues raised as a direct result of this new technology alter both the woman's and the couple's adaptation to pregnancy as outlined in Table 1.

Other examples of points of actual or potential loss and therefore grief, or anticipatory grief, that arise in patients undergoing prenatal diagnosis include: (1) learning that both parents are carriers of an autosomal recessive disorder, (2) learning of fetal death at the pre-chorionic villus sampling (CVS) sonogram (a time when one expected to have an antenatal procedure to ensure that the baby was unaffected), or (3) an abnormal maternal serum alpha-fetoprotein (MSAFP) result in a young, healthy woman who expected her pregnancy to be a time that would proceed smoothly and joyfully. How much we prepare and protect our patients/clients, and ourselves, is always an important and challenging issue.

Preparation for Loss

At the genetic counseling session, much information must be discussed including the indication for referral, the family history and the logistics of prenatal testing. The possibility of pregnancy loss can also be addressed in

TABLE 2. Altered Adaptation to Pregnancy: Points of Loss and Attachment in The Amniocentesis Experience (J. Benkendorf)

Event	Adaptive Response
1st trimester	
1. Confirmation of pregnancy	Acceptance of pregnancy to degree of decision to continue pregnancy
Early 2nd trimester	
2. Pre-amniocentesis counseling	Insulation from hurt due to potential subsequent loss leads to delayed acceptance of pregnancy and even anticipatory grief (tentative pregnancy phenomenon) [6]
a) awareness of procedure-related miscarriage risk	
b) risk of fetal abnormality(ies) assessed	
Early to mid-2nd trimester	
3. Procedure performed	
a) sonogram	Pregnancy suddenly equals baby and becomes a reality, especially for father
I. baby "looks normal"	Enforces dream of healthy baby
II. abnormality detected	Point of loss
b) amniocentesis	Fear of loss due to procedure or fetal abnormality
4. "The wait;" approximately two weeks	Continued detachment, delayed acceptance, guarded emotional investment in pregnancy; all in anticipation of potential loss
Mid to late 2nd trimester	
5. The results	
a) abnormal	Decison-making Grieving process
b) normal results	Equating of normal results on one or two specific tests with normal baby, resulting in greater let down if baby is born with problems undetectable by amniocentesis.
c) sex of baby	Reconciliation of fantasies if not "wished for" sex; naming of baby, elaboration of fantasies, intensified bonding
6. Birth (after abnormal results)	Potentially enhanced coping due to opportunity to prepare for event/loss
7. Birth (after normal results)	
a) good outcome	Reconciliation of fantasies regarding idealized child (normal process)
b) unexpected outcome	
I. death	grieving process
II. birth defect	grief, adjustment—feeling of "betrayal" if test results normal

these sessions and the practices of genetic counselors vary. Given the limitations of time and the best interests of our clients, in what depth should we discuss genetic terminations, miscarriage following prenatal diagnosis, or fetal death detected by ultrasound?

Questions for discussion include:

- Is it helpful/necessary to ask at pre-test counseling what a patient thinks she will decide about pregnancy continuation if an abnormality is detected?
- How many counselors describe the termination process?
- Should patients know exactly how results, especially abnormal ones, will be communicated?
- Should patients be told that a fetal death may be detected by ultrasound prior to amniocentesis or CVS?
- In addition to procedure-related risks of miscarriage, should other issues such as grief and guilt be addressed prior to prenatal testing?
- Should the “loss of the dream” be discussed as some couples will continue a pregnancy after an abnormal or ambiguous result?

Giving Bad News: Fetal Death, Fetal Abnormality or Neonatal Death

There is no good way to convey or receive bad news. How do we make it easier? If the genetic counselor is present at an ultrasound diagnosis of a fetal demise, the loss can be acknowledged, the grief process can be encouraged and support can be offered. The referring obstetrician can be contacted to initiate a management plan for delivery. When the genetic counselor is not present, follow-up options include a note, a phone call or additional support resources such as literature or a psychologic referral.

Communicating information about a fetal abnormality differs at various centers. The genetic counselor, the medical geneticist or the referring obstetrician may make the initial telephone contact. Some counselors prefer to call in the evening to avoid disrupting patients at work, and hoping to reach the couple together. Others prefer to call during the day and offer immediate office consultation.

When delivering news of neonatal death, many factors may confuse the situation. Occasionally the mother is at the birth hospital while the infant is at a tertiary care center. The genetic counselor can improve this situation by contacting appropriate personnel at the birth hospital, such as social workers and maternity care nurses. Awareness that the father may be alone with the infant in intensive care, torn between caring for his child and caring for his partner, can be very important. Although the genetic counselor may not be the individual actually delivering the news, much can be done immediately following by explaining the importance of autopsy, when relevant, making sure photographs are taken of the infant, for the medical record as well as for the parents, assisting the parents with contacting relatives or putting them in touch with support personnel such as social workers and clergy. The genetic counselor also can play an important role in educating the news-givers, or

involved staff, by making books and handouts available, preparing inservice presentations and developing infant loss protocols for both parental support and genetic evaluation [5]. Offering yourself as a back-up consultant or case manager is another way to become more involved. A genetic counselor can also play an important role by giving the family supportive written information about grief or scheduling follow-up appointments.

Grief

How do you describe grief? Much of our theoretic framework for understanding grief is based on the work of Elizabeth Kubler-Ross [7]. Although she worked with people who were dying, the theoretic approach to death described by Kubler-Ross is helpful when trying to aid patients facing a perinatal loss. We now realize it is important not to focus on stages and phases that can be misinterpreted easily by the griever as steps on an upward path that bring them to the top within a few weeks or months at the most, to the place where they were before—reintegration, acceptance. The counselor should share the common reactions and the range of responses parents may experience, ie, difficulty breathing, heart palpitations, not wanting to get out of bed, feeling isolated and overwhelmed, guilt, and/or anniversary/holiday reactions. Some people feel all these things, some just a few and some a variety, often at different times. Most are normal. Unless they are directly harming themselves or contemplating harming others, most people's responses during the first six months to a year are fairly normal. Grieving is a natural process of healing with the long-term likelihood of bringing the bereaved to a "new normal" after much hard work. Grief can be very consuming, draining and intense with short periods of feeling better that usually grow longer over time.

The book and slide show *The Anguish of Loss* [8] were used to share one mother's journey through grief after her son's death. During the year following Justin's death, she sculpted in clay. The resulting sculptures are a touching and poignant portrayal of feelings that transcend cultures, languages, age and history. Most viewers recognize that her process, words, feelings and even the positions of her body reflect what they, too, have experienced.

There are some common gender-based grief patterns. Most men were raised to move on, get back on the horse, get busy, and not to show emotion. This impacts on their outward display of emotion after the loss of a child. In contrast, most girls are coddled, encouraged to use tears and emotions, spend lots of time going over their hurt feelings and do not seem to move on as quickly or easily. This carries over into adulthood. In addition, men are often worried about their partner's health and may function protectively—trying to keep their partner from experiencing more pain. This may be why they do not want their partner to see the baby or be involved in the funeral. When they know she will recover they may feel relieved and not show concern for the

baby. This often confuses the woman who has only been thinking about the baby.

Many men have commented they felt they could let down and really experience their baby's death only after they knew that their partner was going to make it. This often comes at a time months later, when there is little support to start the grieving process.

It is typical for one partner to expect that the other will react, grieve and express themselves in much the same way. If one cries and the other seems cooler and more upbeat, the conclusion could be, "Oh, he doesn't really seem to care. He is over it already." The partner's reaction can then become another loss. This can also occur with other family members who may not be there for the parent(s)—maybe they are distant, emphasizing another pregnancy or reasons to be thankful. Each of these reactions, which do not fit the hopes of the bereaved, often add to the pain of their loss. It might be helpful to ask some open-ended questions to learn about partners' individual family patterns of response to loss. Although these differences often account for maintaining the balance in the relationship, each might need to respect and accept the other's unique coping style and seek support in additional or alternative ways.

Making Decisions

Pregnancy and infant loss of any kind are followed by the need for the family to make many decisions. Deciding whom to tell, how long to stay home from work, and whether to name or bury the fetus/infant can be overwhelming. When the bad news involves a decision based upon an abnormal prenatal diagnosis, the genetic counselor plays an important case management role. Families are overloaded with information, are emotionally stressed and are often not prepared to face the types of medical decisions they must make [9]. The genetic counselor can assist the family through this difficult decision-making process with several skills and options for intervention.

Help them ask the questions they might not think of themselves. Facilitate referrals to other specialists who can provide additional information that may be important in the family's decision. Consider connecting the family with other families who have experienced a similar situation. With both non-professional and professional referrals, it is important to know your referral source so that all individuals talking to the family in crisis are sensitive and appropriate.

Throughout this process, observe the couple's responses for red flags and be aware of other factors in their life. Inquire about their other children, history of previous losses and financial concerns. Facilitate the couple's successful response to the red flag hurdles and assist them in handling these factors.

Prepare the couple for the actual events and details as well as the emotional reactions they may experience. The latter will help reinforce their normalcy

and facilitate the grief resolution. Information about hospital protocols and options can be conveyed so that the family's expectations are appropriate. Possible problems or questions can be anticipated to make the experience less difficult. Help them to anticipate reactions they may face from friends and family during and after the procedure, and help them prepare their responses, ie, what will they tell co-workers at the office.

During the time of decision and loss, many couples have questions about future pregnancies and prenatal diagnostic options. These issues can be addressed to some extent in the period of initial crisis but may need to be reviewed after some time has elapsed. In addition, the variable duration of grief and recovery, often ranging from 6 to 24 months, should be discussed to help prepare couples for the aftermath of termination or loss.

A point on decision-making, I (SI) wish to support the genetic counselors' style of non-directive counseling. Many other professionals seem to put forth their biases, often to terminate the pregnancy since they feel it would be too difficult to carry a deformed or dying child to its natural birth. This unfairly influences parents who need to make their own decision since *they* are the ones who will live with it for the rest of their lives.

Many families have been calling the Pregnancy and Infant Loss Center, sharing stories where minimal testing resulted in the diagnosis of a bad outcome. They often are urged to terminate the pregnancy and "get it over with." Some have been strongly against abortion, highly religious or just could not handle the guilt and fear of having to be the one to decide. A large number felt compelled and cajoled into termination. Many still have regrets and wish that the option of carrying the pregnancy had been more strongly stressed so that they could have decided which was right for them by hearing the pros and cons of both options. I am thankful that genetic counselors do not emulate these professionals, and I encourage you to stand your ground and try to open new avenues to reach those people who are not getting to you in time to make informed choices at this very difficult period in their lives.

Psychologic Well-Being: Creating Memories

Everyone who has experienced the death of a loved one ought to ask, "what do I still have that keeps my loved one alive in my heart and in my family?" The answers always are: memories, photographs, shared experiences with others who knew them. How important are those things to you? Will you let someone take them away so you don't have to dwell on them? Most will say no, of course not. "The memories . . . are all I have, I have been changed because of this person, I do not want to forget them, I wish to remember them. . . ." That is also so with the death of a baby, even a miscarried fetus. If the dreams are real and the future is mapped out, if the love is there, the memories are needed as a part of the healing process. How do you say goodbye to someone you don't fully know? How do you let go when you are so wrapped up, with no

healthy outlet and no opportunity to share with others how much this little one changed you and meant to you? Memories, ceremonies, photographs, sharing dreams . . . this is all these bereaved families have. So little exists of their babies short lives. It is therefore the job of the care providers and family to help create these things that will help in the days ahead.

It is common practice to encourage families to take many pictures of themselves interacting with the dead child (bathing, holding, caressing, sharing with the other sibs. . .). Baptism or naming/blessing ceremonies, collecting mementos such as locks of hair, or foot and hand prints, preparing the family to make their own funeral/memorial service decisions are the things they can do for their child that are becoming more acceptable and available in hospitals throughout the country. Extended family are encouraged to see the baby and participate in these activities during the short time available before the disposition of the baby's body. Babies are being brought home for the family to spend time in a safe, familiar setting before final disposition. In many cases the funeral is even occurring at home where mother, father and sibs can hold the baby during the service and make it a very special time for all.

The need of others, and even the parents themselves, to seek protection from the pain of doing such difficult things is often what stands in the way of people making their own good decisions. Try not to overprotect and make decisions for the family. Rather, advise, encourage, promote, facilitate and support them, while letting them lead the way without the fear of being judged too harshly.

Short-Term Follow-Up and Counseling

In the weeks following the loss, the genetic issues for some families will need to be summarized and reviewed. When additional information is available through autopsy, genetic evaluation or laboratory studies, a counseling visit should be offered to explain the diagnosis, recurrence risks and prenatal diagnostic options. Written information can also be given to the family for their personal records.

In some cases, the diagnosis is discussed in detail with the family during the period of loss. During this period of shock followed by intense grief, it may be difficult for the family to assimilate information. They may choose not to return for further consultation. For these individuals, follow-up phone contact would be advised to review this information and offer emotional support. Letters or pamphlets summarizing medical information as well as literature on grief may be especially helpful.

Grief reactions during this period of time may include guilt, betrayal, relief, anger and depression, with all of their various manifestations. Validation of these emotions can be helpful and can facilitate recovery. Preparing the individual(s) for the possible reactions of family members, friends and acquaint-

tances can assure patients that apparent lack of support may be due to uncertainty and discomfort felt by those in their environment. Families can be made aware that emotional triggers such as encounters with pregnant women, anniversary dates and holidays may produce apparent set-backs in their progress.

Referrals, as discussed in the section on decision making, can also be helpful but may go even further. Every family should feel that seeking care through a mental health professional is very normal and appropriate after such a significant loss. Religious leaders, family and friends may be supportive, however, relationships may change after such a loss. Individuals who are especially supportive may become more important, while relationships with those offering little support may fade.

Written resource materials can be extremely helpful for families dealing with grief resolution. The genetic counselor can assist by providing materials: bibliographies, and reprints whenever possible. The following organizations may also be helpful.

Pregnancy and Infant Loss Center
1421 East Wayzata Blvd.
Suite 40
Wayzata, MN 55391
612-473-9372

National Center for Information on
Maternal and Child Health
38th and R Streets, NW
Washington, D.C. 20057
202-625-8400

The Centering Corporation
P.O. Box 3367
Omaha, NE 68103-0367
402-533-1200

Action therapy focuses on working through grief creatively: to sculpt, write poetry, keep a journal, start a support group, join a telephone network, or become involved in political issues related to pregnancy loss—these can all be helpful. This ability to give back helps families achieve a renewed sense of self-esteem and worth, and also provides a sense that the terrible loss was not for naught.

Long-Term Follow-Up

Involvement in Beyond Prenatal Choice, a support group in the Baltimore/Washington area, has been a tremendous privilege for the genetic counselors

and other professionals. This group started in 1984. Approximately 60 families are currently involved. The professionals are two genetic counselors (GC and JFA), a social worker and a PhD psychologist. The primary goal is to give families the opportunity to talk with other families in a safe place. The consistent, overwhelming grief reaction is intensified because it comes as a surprise to most families who think that the worst is over. They feel a sense of isolation because they may be unable to openly discuss the details of their loss. Families express many of the feelings denoted in our section on grief; however, they do not seem to go through them in a specific order. Anxiety often arises upon considering subsequent pregnancies. This can be a time when many families seek psychological counseling as well as additional genetic counseling.

We have been pleased to hear of other similar support groups.

Care for the Caregiver

To provide adequate support and assistance, it is important for each of us to care for ourselves. Another reason to care for ourselves is to maintain our own health. The patient gets an injection of pain at the time of a loss and the goal for patients is to work that pain through their system. Each time a care provider works with a patient in crisis he or she too gets an injection of pain, only these injections keep coming with each new crisis. Caregivers also need to find ways to work through that pain, and not get discouraged or pretend that the pain will go away by simply ignoring it.

We would like to share the following poem. Thank you for caring for us and our babies.

Thank You

Thank you for the intangibles,
The first touch,
The significant moments,
The searching times,
As long as we live we will bear the imprint of this experience on our lives,
We will ever be sensitized as to the importance of life,
Because of this experience we will live differently.

Precious Parents, 1984.

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Development Of A Peer Support System for Those Who Have Chosen Pregnancy Termination After Prenatal Diagnosis of a Fetal Abnormality

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The discovery of an abnormality in a fetus is a very painful and usually unexpected experience. Often while still in a state of shock and disbelief, and while grappling with complex medical information, expectant parents must decide within a short period of time whether to continue or terminate the pregnancy.

Those who make the decision to terminate suffer a unique type of pregnancy loss. Reactions to this loss vary, and for some people, the support received from family, friends and medical care providers will be sufficient. For others, however, the opportunity to have personal contact with individuals who have made a similar choice will provide needed support and will help to integrate the experience into their lives.

In response to this need, a project was undertaken at the Prenatal Diagnostic Center (PDC) to develop, implement and evaluate a support group program for couples and individuals who have chosen to terminate pregnancies after the diagnosis of a fetal abnormality. Our efforts were based on the premise that the opportunity for patients to focus on common feelings and concerns with others who have been through a similar experience, in a supportive environment where confidentiality is maintained, may represent a crucial component of comprehensive prenatal diagnostic programs.

In November 1987, the PDC staff enlisted the help of Robin J.R. Blatt, MPH, who is the education coordinator for the Massachusetts Genetics Program, and who had offered assistance for such a project in "The Genetic Resource," a bi-annual newsletter published from her office. Four existing programs were reviewed and Ms. Blatt devised an outline with points to consider in selecting a format for the group, phases of development, and tasks to be accomplished.

A core group was established to review materials, set goals, develop a philosophy and coordinate efforts. Initial meetings included Dr. Wayne Miller, the Director of the clinical and laboratory services of the PDC, Dr.

Mira Irons, the pediatric geneticist at the Center, Robin Blatt and Barbara Thayer, a genetic counselor at the PDC.

The major questions that existed at the initiation of our efforts were whether to structure the group based on a peer support system or therapeutic model and whether to set a time limit or allow open-ended meetings.

Reprints, books and articles dealing with the subjects of pregnancy loss in general, and elective termination in particular, were collected and reviewed. Materials from the Loma Linda University support group, "Support for Prenatal Decision," including their training manual for persons interested in providing peer support, the brochure they developed for parents and a videotape for professional education were examined. The materials available from the group entitled "Beyond Prenatal Choice" in the Washington, D.C. area were reviewed. This support group was organized by Virginia Corson, Jill Fonda, Leslie Jadin, Martha MacMillin and Lynda Mulhauser. Their work is described in this volume. Leslie Ciarleglio at the University of Connecticut Health Center, who has initiated a support group called "Hope," and Jodi Rucquoi at Yale, who provides support services for parents who have terminated pregnancies, also provided valuable input.

At one of our initial meetings we had a conference call with Dr. Rayna Rapp, who had conducted 30 interviews with patients who had terminated pregnancies after abnormal diagnoses. From her and from Cathy Romeo, author of *Ended Beginnings*, we learned that closure was important, supporting a designated time frame model. We concluded that we wanted to establish a peer group, including facilitators with backgrounds in genetic counseling, pregnancy loss, and grief counseling. The format of the meetings remained a question.

A group of professionals in the Boston area were invited to meet with the core group to discuss needs assessment, the format for the meetings, facilitator qualifications and backup personnel.

At our first meeting in January 1988, there was a representative from "Cope," a special needs advocate, an educator/grief counselor, a social worker/psychotherapist and an obstetrician who performs terminations. We decided to limit the number of meetings, to initiate sessions periodically and to structure the groups in a self-help mode. After deliberation, this group indicated that they felt the PDC staff would be appropriate as group co-facilitators.

In February 1988 a meeting was held with a social worker who had been active in a Genetics Clinic, a nurse practitioner and an obstetrician who work in an abortion service, a psychotherapist, a perinatal psychologist, another "Cope" representative, and a Planned Parenthood representative. Several informal meetings were held at the PDC with group counselors, social workers, mid-wives and a marriage counselor. We decided that participants in the groups were to be registered. The groups were designed to include from

three to five couples, with two co-facilitators. We debated defined meetings with potential for follow-up sessions, or an initial informational session followed by peer support group sessions.

A letter describing our efforts was mailed to PDC patients in March 1988 to get input from those who had actually been through the experience of terminating a pregnancy after an abnormal result. Patients were asked if they would be willing to fill out an anonymous questionnaire, whether they would be willing to attend a planning meeting, whether they wished to be kept informed of the progress of the group or whether they did not wish to be involved. These letters were sent to 55 people, 27 couples plus one individual. Thirty responses were received.

Fifty percent of respondents replied that an informal short-term support group limited to a few couples or single individuals would be helpful. We received useful input regarding discussion topics. Input was mixed about the meeting format.

In May 1988, Dr. Miller and Barbara Thayer met with a group of patients who had experienced pregnancy termination. There were three couples and one individual present. The consensus was that there was a need for a peer support system, and that the opportunity for patients to interrelate was the critical factor. The group felt that if any information or referral services were to be offered, it should take place at the end of the sessions. The group agreed that the setting of a time limit, as opposed to an open-ended approach, would be more useful. They also indicated that the qualifications of the facilitators were probably not as important as the personalities and capabilities of the individuals. These patients accepted the PDC staff as facilitators and the Center as the location. The patients were concerned that different amounts of time would have elapsed since the termination for those participating in any group. There was a difference of opinion as to whether this would be helpful or detrimental.

The core planners decided that a support group would be initiated approximately every two months, and that sessions would be conducted once a week for three consecutive weeks. A packet of general information in regard to record keeping, ground rules, confidentiality and follow-up meetings was devised. The number of participants in a group was limited to ten, to allow everyone ample opportunity to talk. It was decided that one genetic counselor from the Center and one therapist/counselor from outside would co-facilitate each group.

A discussion topic outline was devised as a guide for the three scheduled meetings. The first meeting would focus on experiences and reactions, the second on communication, and the third on restoring health. A set of communication exercises was developed, and professional and lay press reprints and pamphlets were chosen for distribution to group members.

Facilitators were identified, job descriptions drafted and a reimbursement

fee for facilitators was set at \$100 per night per facilitator. The initial group of facilitators were the three PDC genetic counselors: Barbara Thayer, Kathryn Spitzer, and Bonnie R. Braddock, Isabel Bailey, a medical social worker in the areas of developmental disorders and inborn errors, Barbara Rosenbaum, a medical social worker and therapist, Lyn Billman-Golemme, a registered nurse, licensed social worker, and psychotherapist and Cathy Romeo, an educator, counselor and author.

In September 1988, a facilitator training session was held. At the seminar, the genetic counselors shared information about genetic counseling and their experiences with patients who had abnormal prenatal results. These insights were useful to the other co-facilitators who had not had experience in the field of genetics and prenatal diagnosis. Dr. Alan Altman of the Brigham and Women's Hospital in Boston, who performs termination procedures, spoke to the group about his experience with patients and their physical and emotional reactions to the experience.

At the workshop, the philosophy and format of the group, and the client and provider materials that had been developed were reviewed. Anticipated high-risk situations in the sessions were discussed.

The first series of group meetings was offered in November 1988. An invitation was sent to PDC patients who had terminated pregnancies after learning of an abnormal prenatal result within the last two years. A mailing to Boston area professionals announced the new service and gave instructions for making referrals.

PDC patients currently learn of the group during discussions with the genetic counselors and the physicians at the Center. The genetic counselors mail an invitation to their patients, at an appropriate time after the termination. The PDC also provides laboratory service, and for those patients who receive abnormal results from the PDC via their obstetricians, a letter is sent to the referring obstetrician with the laboratory report reminding them that this service is available. Patients are also referred by other genetic service centers or other medical care providers in Boston.

We have devised a short intake form that is used when patients call the PDC to register for one of the groups. This initial encounter is extremely important. Several group members have indicated that it was very difficult to initiate contact and to plan to attend the meetings. Empathy for their situation and reassurance about the nature and confidentiality of the group put patients at ease.

From November 1988 to September 1989, five support groups were conducted at the PDC. Feedback from participants and co-facilitators has been extremely favorable. Data are being accumulated and themes are emerging. It continues to be a learning experience for the professionals involved and several structural changes are being considered.

The group size was limited to ten, with at least three couples or individuals. The number of people who signed up for each of the support groups was 10, 5, 4, 9, and 7. Of these 35 people, there were 15 couples. Five women attended the sessions alone. In the five groups, only one couple and one husband discontinued participation by choice. Sometimes there were fewer people at the sessions than had registered because of a previous commitment or illness. Although several of the groups were as large as nine or ten members, and two of the groups were as small as four or five, 92% of parents who evaluated the group sessions said that the size of the group was appropriate. Although the dynamics of smaller and larger groups are different, both can succeed.

Twelve of the couples or individuals who attended the sessions had been PDC patients; eight were referrals from other Boston-area centers. One couple attended from Rhode Island. Of the fetal defects that had been diagnosed, 12 were chromosome abnormalities, 5 were neural tube defects, 2 were hydrocephalus, and 1 was a case of Duchenne muscular dystrophy.

The consensus has been that the couples and individuals are pleased to have "found each other." Being able to share their experience with others with a similar experience provided comfort and relief. In general, there was very little need for the co-facilitators to prompt discussion or to provide communication exercises during the meetings. The sessions usually began with individuals and couples describing their experience in learning the abnormal diagnosis, and their experience at the termination procedure. They often had strong feelings, both bad and good, about the care they received. The issues that were subsequently discussed within groups at different sessions varied, but there were some common themes.

The duration and intensity of the grief had been surprising to many individuals. The degree of trauma was reflected in the number of couples, who in addition to attending the peer support group, had been to marriage counselors, psychiatrists, therapists and grief counselors. Couples found it reassuring to find that others were reacting with the same intensity.

Another major issue was the difference in male and female reactions to the pregnancy termination experience. Common points were that females had to deal with the added component of experiencing the physical aspects of the pregnancy and termination, and that their reactions seemed to be more intense. The effect on sexual relations was a common issue, as was the difficulty of receiving results that were not "100%," for instance, the presence of a *de novo* marker chromosome in fetal cells or the prognostic difficulties in a case of spina bifida. The process of making a decision based on information that did not have a high degree of certainty was extremely difficult for several couples.

The implications of having people for whom various amounts of time had elapsed after their termination in the same group had been one of the main

issues raised by the core group and facilitators. The time spans in the groups varied widely. Discrepancies in time elapsed led to very helpful discussions about the stages of grief and the variations in timing and sequence of grief reactions. Some of the couples who had suffered their loss more recently were encouraged by other couples' progress.

Some patients had questioned the advisability of having participants with and without children in the same group. This particular situation has posed no great difficulties. There were two groups in which all participants had at least one child. Issues discussed included a fear of harm coming to the children and the great comfort that children give their parents during a time of loss. In the other groups, there was a mix of participants with and without children. The issues seemed to be kindly and gently discussed within the groups with patients recognizing the comfort that children can give and the special grief of the several patients with histories of infertility.

There was also discussion of how pregnancy termination could revive feelings about other losses experienced in the past and raise unresolved grief issues. Another theme was the universality of human need for help in dealing with tragedy.

Issues relating to future pregnancies were often raised by participants. There frequently was real fear of being placed in the same decision-making position again. Participants were comforted that other people shared the same thoughts and feelings and therefore felt more prepared to undertake another pregnancy. At this point in time, 35% of the couples or individuals who participated in the groups have begun another pregnancy and we have been in contact with most of them.

In general, support, acceptance and attachment were obvious in each of the groups. There was a sense of permanent connection and real progress. The reluctance to leave when the sessions were over was obvious. A follow-up meeting was requested in four of the five groups. Couples indicated a need to meet again after some time had elapsed. Participants in the group often exchanged telephone numbers and addresses and several of the groups had informal outside meetings. People who attended the sessions agreed to talk on the telephone to other couples who terminated a pregnancy.

We received 26 written evaluations from the 35 people who attended the five support groups; 96% stated that it was very helpful or somewhat helpful to participate in the support group. The one person who said it was not helpful stated that he did not feel the need for any additional support and that he had attended because his wife had insisted. He added that the group assisted him in understanding some of his wife's feelings.

Eighty-five percent of participants felt that a two-hour session was suitable; 12% felt that it was too short. The biggest split was that 54% of participants felt that the three sessions were adequate, 46% felt that three were too few.

The participants indicated that the reprints were very helpful. These materials consisted mainly of articles written by patients who had had a termination and who wanted to share their experience in the lay press. This reaction was understandable in light of the participants' obvious eagerness to meet or to learn about other couples who had been through similar experiences. Professionally produced brochures were also appreciated.

The co-facilitators were asked to evaluate each session in writing. In general, the co-facilitators have been impressed with the intensity and productivity of the sessions. They felt that the experience of co-facilitating was very satisfying. They were impressed with the sharing that took place and the bonding that developed within the groups.

The genetic counselors found working with the groups to be a valuable experience. The opportunity to work with other professionals, and the complementation of expertise brought to the setting by the genetic counselors, therapists and social workers is impressive. Having genetic counselors present at the sessions is critical because they have dealt with abnormal prenatal diagnostic results and have experience in counseling individuals and couples faced with decisions about pregnancies. The experience of the other co-facilitators in group counseling, marriage counseling and pregnancy and loss counseling is an important addition. The cooperative effort has served to develop a network for referrals.

Evaluation of the project is ongoing. The format of the sessions is under review. The verbal and written feedback indicate that three sessions may not be adequate. Alternatives include scheduling more sessions, monthly or bi-monthly meetings after a set of sessions or reunion type meetings. A related question is whether to continue after the scheduled sessions with a discrete group, or whether to funnel participants into meetings that anyone who has participated in a group can attend. We do feel that it is important to register participants and to have them work as a group for a set number of sessions before transferring them to generalized meetings.

Another idea that is being considered is allotting a time within the sessions for men and women to meet separately. Feedback from participants has indicated that such time may be useful for sharing particular concerns that may be more paramount to males or females. We intend to try this exercise at some of the future sessions and evaluate its usefulness.

The support group has been named "AfterWords" and a brochure is being printed that can be given to patients. A supply of the brochures will be mailed to genetic centers and other professionals in the Boston area. This mailing will also serve as a reminder that the support group is available.

An issue that needs to be addressed is future funding. For the first year of our efforts we had received a grant from the New England Regional Genetics Group. This money was used mainly for compensating the professionals and

for clerical work and supplies. The PDC will now provide the salaries of the co-facilitators, but alternative funding sources will be explored.

In summary, organizing and implementing the support group have been very satisfying for the counselors and the other co-facilitators. Group participants indicated that the opportunity to meet with other patients who have terminated a pregnancy is an extremely helpful experience. Many of the participants indicated that before entering the support group, they had never met any individual or couple who had been faced with a similar decision. The need for contact was highlighted by a couple who had been attending a pregnancy loss support group for two years, but who had never shared the true story of their experience, always describing their loss as a miscarriage. The opportunity to openly share experiences and feelings in the "AfterWords" group was very important to them in relieving what was described as 'the burden of secrecy.' One patient, in her evaluation of the support group, wrote, "The group is of great value, and its existence is so very necessary in ultimately achieving resolution and closure after this most arduous of experiences." Making a support group service available to individuals and couples who have terminated a pregnancy after the diagnosis of a fetal abnormality is an extremely important component of any comprehensive prenatal diagnostic program.

A Protocol for Genetic Counseling Following Abnormal Prenatal Diagnosis

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INTRODUCTION

Prenatal diagnosis for a wide range of genetic disorders has been available for two decades. Thousands of women have undergone these procedures. Approximately 2% of these women receive abnormal results and consider termination of the pregnancy. The total number of women in this situation is significant and their management should be recognized as an important aspect of health care. Skillful and timely counseling for both parents following the decision to terminate a pregnancy due to an abnormal result may be critical to coping with these tragic events. Unresolved feelings interfere with the resumption of one's daily routine, tend to perpetuate and intensify the grief reaction and may disrupt the marriage. The genetic counselor can play an important role in providing information and support, coordinating care with physicians and other health professionals and advocating for the patient. The purpose of this paper is to describe a protocol for counseling patients and their partners from the time of diagnosis through the mourning process.

PRIOR TO DECISION

Goals: Facilitate decision-making. Interpret and provide medical information. Provide grief counseling. Provide supportive counseling.

Informing the patient. Call the obstetrician to plan who is going to inform the patient. It is usually decided that the counselor will do this. Call the patient in the evening to maximize the chance that both parents will be home. Explain that an abnormality was discovered and try to defer details of the diagnosis until you can see them in person. Make an appointment for the following day. Inform the obstetrician and medical geneticist about the appointment and invite them to be present at the session.

Informing session. Present diagnosis, range of severity and prognosis. Avoid being directive or judgmental. Tell the couple that there is time to think

it over (if there *is* time) and discuss the advantages and disadvantages of waiting. Encourage patients to discuss the pros and cons of termination vs continuation of the pregnancy. Nothing further can be done until a decision is made.

Decision. Validate their reasons for making this decision. If they decide to terminate the pregnancy, talk to obstetrician about arranging admission.

FOLLOWING THE DECISION

1. If the couple decides to terminate, describe the procedure. Termination procedures vary among institutions and among obstetricians within the same institution. Familiarize yourself with the details of these procedures, including side effects and complications. Be prepared to discuss them with the patient. Every effort should be made to provide a private room on a non-maternity floor for the patient. Confer with the postpartum nursing staff and labor and delivery units. Attempt to make arrangements for the husband to stay overnight.

2. Mention options of seeing/holding the fetus, obtaining photographs, having a baptism, autopsy and burial. Warn the patient of possible signs of life in the fetus. If the baby is born alive, it will be taken to the NICU and made comfortable until it expires. Birth and death certificates will be issued and the baby will be buried. Parents may select private or city burial. City burial entails an unmarked grave. If the fetus is less than 20 weeks' gestation, burial is optional. Involve the clergy if the patient wishes.

3. Delivery. Instructions should be given to the obstetrician, labor and delivery staff, etc. re samples needed for studies on fetal tissue.

4. Prior to discharge. Provide anticipatory guidance regarding the following issues: 1) postpartum emotional and physical reactions of couples in their situation, ie, stages of mourning, effects of hormonal changes, etc; 2) recovery may not be as smooth as expected; 3) normality of their feelings. Encourage open communication. Discuss the difference between male and female reactions and what to tell their friends and older children. They should expect insensitive comments from people. Counsel along the lines of the "stages of mourning." It may be necessary to raise these issues before and after discharge. Schedule a return visit.

FOLLOW-UP VISITS

Evaluate patient for loss of appetite, insomnia and other signs of depression. Consider psychiatric referral. Explore issues surrounding guilt, blame, "Why me?", God/religion and shame. Offer to introduce them to a couple who has

terminated for genetic reasons and give them information about termination support groups. Send letter to obstetrician summarizing counseling.

COUNSELING TECHNIQUES TO FACILITATE DISCUSSION OF ISSUES

I. These questions may help elicit their feelings about the termination experience; keep in mind that not all of these are issues for every couple. How are they getting along? (Keep probing, even if they answer "Fine").

What was the worst part of their experience?

What was the best?

Who was the most/least supportive?

What, if anything, surprised them about reaction of family and friends?

How would you have liked them to react?

What have/are you going to tell your friends?

If they want to tell people about the termination, rehearse them for how to tell people. Prepare them for people's reactions. Discuss the fact that they may want to avoid their friends because the initial confrontation may be painful. Explain that after the initial meeting, this will be over with and they can benefit from their friends' company and support. They need support from people who care. Don't avoid friends for an extended period of time and risk isolation and losing friends.

II. How do your feelings compare to your spouse's feelings? Patients should consider the differences between the husband's and wife's post termination reaction, ie, bonding, hormones, daily routine, physical state, sexual activity, grief, "emptiness." A crisis like this either could bring them closer together or push them further apart.

III. If the woman has had a previous elective termination, how does that experience compare to the current termination of this abnormal fetus? Ask the patient to verbalize how the decision was made.

IV. Validate their decision: What would have been the burden on them? What would have been the effect on their normal children? What would the affected child's life have been like? Encourage or support the feeling that they had no choice but to terminate. Emphasize that no one can put himself in their place and say what he would have done.

V. What impact has the termination had on their children? How do they deal with their grief in front of the children? Prepare them for the possibility of later reactions/sadness. Suggestions for parents in dealing with their children:

- 1) Be honest but keep explanations simple and at a level commensurate with their ability to comprehend.

- 2) Include them in your grief. If you pretend everything is fine, they will sense things are not fine anyway. You may deny them their need to grieve.
- 3) Encourage them to express their feelings. Reassure them that:
 - a) this can't happen to *them*;
 - b) mommy and daddy aren't going to die;
 - c) they didn't cause it.
- 4) Do not implicate the hospital as a place where children go and never return.
- 5) Do not assume that if they aren't talking about it, they aren't thinking about it. Bring it up if they don't.

VI. Some women, especially in the first few days after the procedure, think it has all been a bad dream and expect to wake up and find that everything will be fine. Did they experience this? After this experience, their emotions are in such turmoil that they may feel they're going crazy. Reassure them that they are normal people experiencing intense emotions they may never have felt with such strength before.

CONCLUSION

Regardless of the patient's educational level, occupation, or socioeconomic background, the response to abnormal prenatal diagnosis is remarkably universal. When the patient first receives the news, she enters a crisis period. Her greatest need is for information. She needs to know what her results mean, what her options are, and, if she chooses to terminate, what that procedure entails. The counselor may be the primary provider of the information. After the termination, her greatest need is to resolve the psychologic issues surrounding the crisis. These can be dealt with at a slower pace as set by the patient. In this stage, the counselor needs to say very little and listen empathically. In this environment, the issues addressed here often surface spontaneously and without prompting.

Group Counseling For Couples Who Have Terminated A Pregnancy Following Prenatal Diagnosis

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INTRODUCTION

Prenatal diagnosis for a wide range of genetic disorders has been available for two decades. Thousands of women have undergone these procedures worldwide. Approximately 2% of women whose pregnancies are subjected to such testing experience abnormal prenatal diagnosis results and consider termination of the pregnancy [1]. The total number of women in this situation is significant. While the medical and lay literature include many references to psychosocial responses and psychotherapeutic needs of women who have experienced perinatal death and abnormal livebirths, much less attention has been directed toward the emotional response and needs of women and their partners to the termination of a pregnancy due to abnormalities in the fetus. There is, however, a growing awareness of the importance of a support system for these individuals. Existing support groups for couples grieving because of infertility, miscarriage, stillbirth or death of a child do not adequately meet the needs of this special group. Factors that contribute to their unique requirements include the implications of the *decision* following prenatal diagnosis, the *genetic factors* inherent to most cases and the sense of *isolation* [2]. The purpose of this paper is to describe, in practical terms, a group counseling program for women and their partners following a decision to terminate a pregnancy for genetic diagnoses.

THE GROUP COUNSELING PROGRAM

Group Composition

During an eight-year period, there was a total of 82 referrals, which originated from the following sources: 49 (59.9%) by staff at the hospital where the groups were conducted, 30 (36.7%) by colleagues at other institutions, and three (3.8%) self-referred because of features about the group in the media.

During the past two years for which statistics are available (March 1987 to

March 1989) 23/44 (52.3%) patients referred refused counseling for various reasons, including the belief that they could cope without the group, interval between referral and group availability, preference for another form of therapy, another pregnancy in progress, transportation problems or conflicting work schedules. It should be emphasized that the interval between groups was sometimes several months due to insufficient referrals.

Fifty-five family units, 35 couples and 20 single women, attended a group counseling series. There was a high degree of concordance for demographic factors: 97% of participants were caucasian, 3% were other races, 50% were Jewish; 77% reported family incomes in excess of \$25,000; 35% had some college education, and 50% had graduate degrees or were working toward a degree.

Group Organization

To generate a sufficient number of participants to begin a group, networking for referrals was required with allied health professionals in other hospitals. Applicants were eligible for the group if they had made a decision to terminate a pregnancy following prenatal diagnosis.

A group was required to have a minimum of eight individuals. Participants were required to attend a pregroup private interview. The fee for the series of group counseling meetings was payable at this time, but no one was excluded for financial reasons. A letter was sent thanking the referring professional and providing information about the dates of the group counseling series and precounseling interview.

Meetings were 75 minutes, weekday evenings for six consecutive weeks. Male partners were encouraged to attend. Women without partners were urged to attend alone. The same private conference room was reserved for all meetings. Since some people find it painful to return to the hospital where the termination procedure took place, an off-site location was provided, when possible.

Groups were conducted by one genetic counselor. All sessions were recorded, with the permission of the participants, for future reference and teaching. Requests to interview couples or to observe meetings were strictly limited and allowed only with the permission of the group. Once a group was in progress, new applicants were placed on a waiting list. In the interim, they were offered individual and peer counseling.

Group Counseling Techniques

General counseling methodologies. At the beginning of each session, group members were given the opportunity to introduce issues. The counselor functioned as a facilitator and avoided individual counseling. Comments directed to the counselor were redirected to the group whenever possible.

Tangential issues were noted for future discussion so that the main topic could be resolved. Topics that were "on reserve" were reintroduced by the counselor when appropriate. The counselor utilized reflective responses to direct attention to themes of general interest. Information and insights gained from the private pregroup meetings allowed the counselor to utilize subtle strategies for group interactions relevant to individual problems. The group was encouraged to share difficulties as well as solutions regarding problems.

Couples were assisted to understand disparate feelings about the prenatal diagnosis, termination of pregnancy and phantom baby. Methods likely to enhance communication and understanding were explored. Support among group members of the same sex was utilized as a strategy when appropriate.

The counselor was watchful for the potential for harm as the result of contrasting circumstances among group members, or particular remarks. Reports of increasing stability between group meetings were interpreted as signs of progress. At meetings that followed the halfway mark in the series, some discussion was directed toward function when group support would no longer be available.

First meeting. Each participant was provided with a stand-up nameplate and seated either in a circle or at a round table. The counselor avoided sitting in a singular position. Participants were introduced as they arrived.

The counselor's opening remarks. The counselor proceeded with a warm, empathic greeting in which there was reference to the shared tragic history and acknowledgment of the ambivalence of some and urgency of others regarding attendance at the meetings. Participants were reminded that the group setting provides a protected environment to share feelings unlikely to be understood elsewhere. Participants were urged to save troubling feelings for discussion at the meetings. The acute grief and torment currently affecting group members was defined as a normal but stressful response. Reference was also made to the failure of some family members and friends to recognize the need to mourn for the loss/death of a baby/fetus, to allow that the period of mourning might be lengthy and to adequately provide emotional support for the bereaved parents (Black, personal communication). Group members were cautioned that the goal of the group meetings would be to lessen their grief. Sad memories could replace acute pain. They were cautioned that the actual tragic experience could not be erased by group counseling or by any other means.

The counselor explained that she would monitor the meetings to avoid monologs or fragmented discussions. Participants were told that they could contact the counselor or, with permission from one another, other group members between meetings. Group members were instructed to attend every session and to arrive promptly. The group would not work well without all its

parts. Each group member was then asked to describe his or her history and reason for joining the group.

Final meeting. The group was offered a final opportunity to introduce new topics. Participants were asked to compare their emotional status at the first meeting and final meetings. If group members indicated that they would like to continue meeting on their own, an address list was provided (this was sometimes requested during the series) and they were encouraged to utilize the group structure as long as it was beneficial [3]. Group members were asked if they would be willing to serve as peer counselors. The counselor's closing remarks always reflected warm regard, respect for and confidence in group members. They were encouraged to request individual counseling and to remain in touch. A letter was sent to each participant with a similar message.

Post-group. Former group members become part of the counselor's ongoing case load with occasional telephone calls and appointments for support, sharing relevant articles, visiting with new babies, etc. Many alumnae continue to view the counselor as a significant person in their lives, associating the counselor with their achieved positive readjustment to life.

COUNSELING ISSUES

The following issues were invariably introduced by participants.

Communication of results. Preparation for abnormal results was discussed. For example, some people had premonitions that "something was wrong with the pregnancy" while others felt totally unprepared for bad news. The professional who communicated the abnormal results was the focus of anger in some cases, while others expressed gratitude for sensitive and empathic treatment. Physician or hospital bed availability sometimes determined that several days elapsed between results and admission to the hospital. For some people, this was a welcome interval to "say good-bye" to the baby or confirm the decision. For others, waiting was intolerable. Most preferred immediate admission [2, 4].

Factors relating to the decision. Considerable discussion centered on feelings about the decision to terminate the pregnancy. Factors included the implications of the diagnosis, particularly with regard to the expected quality of life. Other factors included religious and ethical beliefs, advice and support of family, friends, genetic counselor, physician and clergy.

Participants revealed varying degrees of guilt and confidence regarding the decision to terminate the pregnancy. Frequently, individuals spoke with emotion concerning the conflict between previously held attitudes concerning abortion and the sacredness of life and the decision to terminate a pregnancy because of a lethal, handicapping or "prognosis uncertain" diagnosis [4].

Couples thought about whether they had "lost a pregnancy" or had decided that a less than perfect fetus/baby should not be born. For many diagnoses, the parents felt that they had no choice because the prognosis was so severe. The decision was never considered trivial and always was experienced as tragic. Despite the conflicting emotions, the overwhelming majority of individuals believed that their decision was correct because it avoided suffering on the part of the child, parents and extended family [4].

Many people struggled with the frustration of finding no answer to the question, "Why did this happen to me?" Some people could accept odds, others assumed that they were being punished or treated unfairly by fate. Men, in particular, had difficulty dealing with the loss of control over an important life event, ie, an irreversible diagnosis.

Experiences related to the termination procedure. In the first meetings, women in particular needed to discuss the termination experience. Comparisons were made among women. Positive and negative experiences were related regarding the attitudes of nursing staff and other health professionals to the reason for their admission. Most women were treated with kindness, but some were distressed by judgmental behavior or association with teenagers and others terminating unwanted pregnancies. Women greatly appreciated the availability and effectiveness of staff familiar with a "bereavement protocol" [2]. Women who had terminated in settings where these services were not available felt disadvantaged. There was a great deal of expressed sadness about going home without a baby and in many cases a sense of unreality about ever having been pregnant. Women described the sense of 'emptiness.' Physical postpartum signs were extremely distressing. Some men felt that no one was concerned about their feelings.

An important issue was whether the obstetrician fulfilled the patient's expectations during the hospital admission and interval between discharge and first office visit. Decisions about continued care by the same physician hinged on these experiences.

Coping with life after the termination. Couples carefully considered to whom they wished to confide the true facts. Did they want to risk being the recipients of value judgments from people who had never had the same experience?

Reactions of family and friends were described. They suspected that relationships would be permanently altered because of disappointments. Many women had great difficulty seeing pregnant women or new mothers with babies.

There was agreement about the unacknowledged need for a formal mourning period. There was a reported discrepancy between the need to grieve for a *baby* and the assumption by others of a 'recovery' from a failed *pregnancy* in

an arbitrarily designated, usually brief, time period [2], (Black, personal communication).

Couples had difficulty dealing with the differences between parents in bonding to the fetus and grieving, which probably were related to biologic and psychologic facts [2]. A shared tragic experience brought some couples closer, while others felt that their relationship was threatened (Black, personal communication). Couples needed help with children old enough to be informed of the decision, or aware of the failure of the pregnancy and/or the parents' grieving. Some people expressed a new sense of vulnerability defined as a significant fear of the loss of other family members.

A common dilemma involved the decision to conceive again. Most people were afraid they would experience another abnormal diagnosis. Even normal prenatal diagnostic results would not preclude anxiety regarding undetected defects. Also, some couples felt that they were deciding afresh about the impact on their lives of a new baby.

CONCLUSIONS

Genetic counselors are unique professionals who can provide information about medical genetic diagnosis or birth defects as well as counseling for the response to this information, which includes bereavement counseling.

Inservice education should be made available to medical and allied health professionals who could provide sensitive care to this population of patients during the admission for termination and posttermination periods and also serve as referral sources. Opportunities should be sought for exposure in the media or through public health channels to inform women of the availability of group counseling services.

Skills applicable to individual genetic counseling must be modified for group counseling. The counselor's goal is to have the group members respond to one another by orchestrating the flow and direction of the discussion and by providing the input that keeps the group on track without allowing the discussion to be processed via the leader.

Efforts should be made to provide routine genetic counseling for all patients prior to prenatal diagnosis. Most patients feel that the information, counseling and introduction to a counselor who will continue the process after the diagnosis aids preparation for the decision-making experience.

The genetic counselor should be prepared for powerful emotional sessions. Previous experience with psychologically oriented individual counseling may not prepare a counselor for some particularly intense discussion.

The counselor's reward is that most participants find considerable relief and a sense of being able to get on with their lives even though they are not free of their sadness. Group counseling seems to be a valid support mechanism for

individuals and couples who have experienced a pregnancy termination following an abnormal prenatal diagnosis.

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Known Fetal Malformations During Pregnancy: A Human Experience of Loss

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INTRODUCTION

Historically, the diagnosis of a major birth defect or malformation was made at birth or at some time during the first year of life. The growth in reproductive technologies has included alpha-fetoprotein determination, real-time ultrasound, amniocentesis and chorionic villus biopsy. Along with new methods for diagnosis, new fetal therapies have arisen such as enzyme replacement and fetal surgery. These specific technologies in diagnosis and treatment have been well described in the literature; their impact on reproductive families increasingly is being addressed by researchers such as Sandelowski [1]. Beyond a few isolated reports, such as Grubb's description [2] of a woman's experience of carrying a dead fetus, Costello's work [3] with known fetal abnormalities, and reports dealing with pregnancy termination following a genetic diagnosis [4-6], there have been no specific studies of the impact of known fetal malformations on families during pregnancy.

Between 1981 and 1984, ventriculoamniotic shunting procedures were performed in Denver on four fetuses. These highly publicized procedures provided an impetus for physicians to send pregnant women to the medical center for evaluation and intervention when fetal abnormalities were suspected. In over 99% of the families seen ($n = 135$ cases), there were no available therapies. These families, who now had a great deal of information, but no treatment options available to them, are the focus of this investigation. The goal was to explore the human experience of knowing that the pregnancy would most likely end in the baby's birth and death. The following research question was asked: *"What is the pregnant woman's experience of knowing the baby within has a major malformation?"*

METHODOLOGY

The qualitative methodology of phenomenology was selected as the theoretical basis for the study, since the purpose was to understand and describe the experience of known fetal malformations from the perspective of the women who had "lived" this experience. As Oiler [7] states: "Phenomenological

description is simply the effective communication of insights into human experience." It is the notion that insight allows one to discover rather than to verify preexisting notions of reality.

The phenomenological method described by Swanson-Kauffman and Schonwald [8] was used in the investigation. It consists of four basic strategies—bracketing, analyzing, intuiting, and describing.

A convenience sample of 20 women, who had been evaluated for fetal malformations, consented to participate. A planned cross-sectional design was employed (Fig. 1). Five women were pregnant at the time of the interview. Of these, 3 were interviewed 2 weeks following the evaluation and 2 were interviewed 6 weeks postevaluation. Fifteen women were interviewed at various times from one month to 17 months following delivery.

Gestational ages at time of diagnosis ($n = 20$) ranged from 12 weeks to 38 weeks. Gestational ages of the infants at delivery ranged from 16 to 39 weeks. The period of "preparation," ie, the amount of time from diagnosis to delivery was 0.5 to 11 weeks, with a mean waiting time of 4.2 weeks. Two of the women chose a "planned birthing," (a pregnancy termination). One of the women went into spontaneous labor the morning of her planned birth; the other had labor induced. The term "planned birthing" was specifically chosen as these women never referred to their decisions as terminating the pregnancy, but rather inducing labor early. They also held and named their babies after delivery.

Sociodemographic data (Table 1) indicate a population of predominantly white, middle-class females. The age range of these women is 20 to 32 years. None of these women would have been candidates for genetic amniocentesis. All the fetal abnormalities were originally suspected on ultrasound. The initial reasoning for doing the ultrasound varied, ranging from a routine assessment

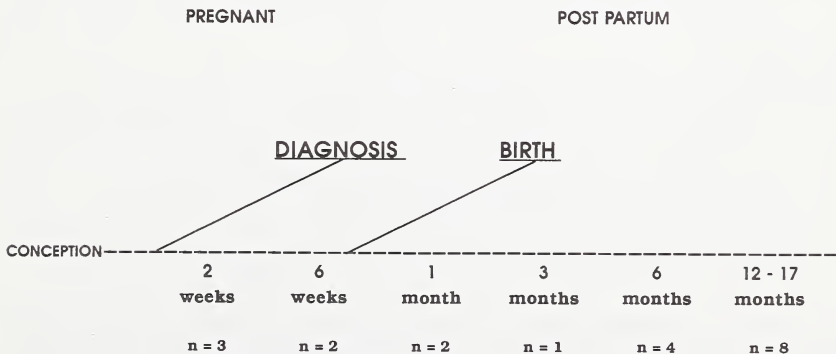


Fig. 1. Cross-sectional design of recruitment for study.

TABLE 1. Sociodemographic Data

Variable	Range	Mean
Age (years)	20–32	26.4
Education (years)	11–16	13.4
Annual gross income	\$2,000–60,000	\$21,908
Ethnicity		
Caucasian	16	
Hispanic	4	

to concern for a decrease in fetal movement, or abdominal size not congruent with gestational age.

Fetal malformations diagnosed included chromosomal abnormalities, central nervous system malformations (CNS), gastrointestinal and renal abnormalities. Of the 21 infants born to the informants (there was one set of twins), 19 died shortly before delivery or within the first day of life. One infant with trisomy 18 lived four days; the infant with hydrocephalus was born following a cesarean section and survived the neonatal period.

Interviews were conducted in the informants' homes and were tape recorded. Informants were asked to "tell me what led up to your referral to the medical center for evaluation" and "what were your thoughts and feelings when you knew the baby inside you was malformed?" The recordings were then transcribed verbatim. Seidel and Clark's *Ethnograph* [9], was used to sort, code and retrieve data.

In an attempt to verify the model generated from the data, a nurse researcher uninvolved in the study randomly selected interview transcripts to ensure that the data fit the categories described. Experts (a genetics clinician, a bereavement specialist and a woman who had been evaluated for fetal malformations) were asked to critique the credibility of the emerging model from their perspectives.

FINDINGS

The Expectancy of Loss model (Fig. 2) consists of the phases of *Uncertainty*, *Verification*, *Preparation*, *Reconfirmation*, *Reparation*, and *Resiliency* that occurred over a period of time from suspecting to thereafter. The wavy line represents the human response curve—a visual depiction of the emotional intensity described by the informants—the nexus of numerous emotions such as shock, pain, hope, fear, relief and despair.

The model begins with *Uncertainty*—the suspecting phase that all was not well with the pregnancy. Some informants had "premonitions" that something was wrong, others were not aware until their health care provider stated "you're big for your dates, let's do an ultrasound." Informants described their initial reactions as "shock, fear, panic, confusion, disbelief." All informants

UNCERTAINTY VERIFICATION PREPARATION RECONFIRMATION REPARATION RESILIENCY

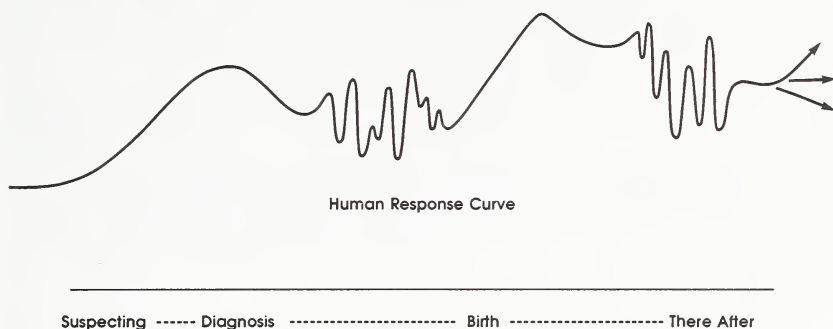


Fig. 2. Expectancy of loss

agreed that waiting for *Verification*, whatever the time frame, was much too long.

"I wanted to, just to get down there immediately and that was so hard. That waiting. Even though it was only a day . . . it was a nightmare, it was like you were in slow motion. Even though you were, things were happening so fast. . . ."

Verification was the "fact finding" phase—the actual evaluation process to verify the nature of the malformation and its prognosis. This included discussions of diagnosis, prognosis, options available and decisions regarding the next step. For most informants the initial response was: **FIX IT!** As one woman so aptly stated: "OK, give him the pill and it will be all better!" If the prognosis was interpreted to be "lethal," then the immediate response was to "get rid of it"—or they wished they could "get rid of it." "I'd just as soon get it over with instead of prolonging it." The informants also expressed "Why Me?" and "What did I do to make this happen?" A typical statement:

"I guess maybe I thought it was something that we did wrong—you know, I drank or ate something—too many vitamins or not enough or maybe it was the Tylenol I took for my headaches. . . ."

The waiting game or phase of *Preparation* was the time from evaluation to delivery. It was overwhelmingly characterized as a hope/no hope cycle.

"You sort of hope for the best no matter what. I feel we're doing the best we can." was a typical statement.

The informants described this time as an emotional roller coaster or seesaw—emotions were in constant flux as they either discussed what they might do, such as whether or not to see and hold the baby after delivery, or took specific actions to prepare for the birth/death of the baby. One woman

spent the weekend planning funeral arrangements, which she stated was very difficult as the funeral home director just could not understand her actions since she was still pregnant. She delivered a stillborn infant with achondrogenesis four days later. Finally, informants used this time to seek out support from their spouses, relatives, friends and/or health professionals.

For the 15 women who had delivered at the time of the interview, the phase of *Reconfirmation* was the revalidation, the living reality of the severe nature of the infant's abnormality and the eradication of the "hoped for miracle." It was the culmination of the thoughts, feelings and perceptions that had been intensifying steadily from the first moment of suspicion. The birth was often met with a sigh of relief that the "waiting" was over. Definitive action replaced speculation—the question "do I want to see the baby?" was replaced with, "Yes, I want to see him or I want to hold her."

Although each birth and death was a unique experience, informants shared several similar views of the experience—seeing, holding and naming the baby, reactions to the abnormality, reactions to the infant's death and decisions about funeral or memorial services. Thirteen informants saw and held their infants; almost all discussed the infant's "good points."

"He had a really pretty nose . . . it was just a beautiful little baby. He had a lump in his tummy that needs to be fixed. . ." (The infant died with gastroschisis.)

Reparation was the process of "readjusting," rebuilding a normal everyday life. Informants described returning home with empty arms, putting away the nursery, dealing with the production of breast milk, seeing other infants and having every waking and sleeping moment centered on "my baby that died." They spoke of the importance of acknowledging and revalidating the birth and death of the baby, of building memories with pictures or a lock of hair.

" . . . it's not a memory. There's some proof there that . . . it's not a dream."

Readjusting was also seen as a time to reevaluate relationships. Most of the informants stated that the experience brought them closer to their spouses because of having shared it together.

Finally, readjusting became the time that informants found themselves to be more up than down and moving on. For those women who identified a "turning point" in their grief, returning to work, receiving autopsy results and genetic counseling were found to be the most helpful events.

The final phase of the model was *Resiliency*—the time to "hope for the future." The hope was most frequently translated into considering future pregnancies. Of the 15 informants who had delivered, one had just delivered a normal boy, 3 were currently pregnant, 1 was actively trying to become pregnant, 7 were considering it in the future and 3 had taken permanent steps to prevent pregnancy (these 3 informants each had 2 or 3 normal children).

Informants generally considered their "risk" for problems in future pregnancies to be low, but all were or would be monitored.

In ending the interviews, all 20 informants were asked if they were glad that they knew that the baby had problems prior to delivery or would it have been better not to have known? The overwhelming response from all the informants, both pregnant and delivered, was Yes, even though "knowing" was extremely difficult—it was the lesser of two evils.

"I don't know. I'm torn. I think this allowed us to prepare for what was going to happen. I think . . . it would have been devastating to find out at nine months. So . . . as hard as it was, I'm glad we knew ahead of time."

CONCLUSIONS

The major implication gleaned from the model generated from the unique and varied experiences of 20 women who knew during their pregnancies that their fetuses were malformed was that the information received during counseling throughout the process had a positive impact on the experience.

First, it provided information upon which decisions could be made. While almost all the women maintained a "hoping for the best" attitude, decision-making efforts and choices increased their perception of control in an uncontrollable situation. Choices ranged from decisions regarding pregnancy status (termination, fetal therapy, wait and see), care of the infant at delivery, and postdelivery decisions (naming, seeing, holding the baby, photos, funeral).

Second, it allowed for the initiation of anticipatory grief reactions. The foreknowledge of the presence of the fetal malformations allowed the women and families to begin their grieving process *before* delivery. Labor was often viewed as a relief and the malformed infant was most often looked upon with sadness and emptiness instead of shock and disbelief. The grieving process, while appearing to be shortened from *Reconfirmation* (Delivery) to *Resiliency* ($X = 3.6$ months), in fact, remained toward the published norms of Lindemann [10], Parkes [11], and Marris [12] of 6–12 months when the grieving period included the period of *Preparation* ($X = 6.8$ months).

Third, information given to families during *Verification*, *Preparation* and *Reparation* was interpreted as a factor in decreasing guilt and blame. Women stated that the information provided them was extremely reassuring and helped to dispel initial reactions of "What did I do?"

"... If anything, they helped me understand more . . . about the genetics side and . . . I think if I wouldn't have had them to explain certain things to me, I might have thought something in my blood line caused this or something. But I see now that it didn't. So, they were very, very helpful."

Finally, the knowledge that the physicians were informed ahead of the

delivery and were prepared was very reassuring. "Everything that could have been done was done."

RECOMMENDATIONS

The following recommendations are made based on the data generated from the experiences of these 20 women:

- 1) Provide as much information as possible prior to delivery regarding options, possible outcomes and infant care after delivery.
- 2) Assist the family in memory making: seeing, holding and naming the baby, photographs, funeral or memorial arrangements.
- 3) Anticipate grief reactions *prior* to delivery and assess need for intervention if these reactions are absent or inappropriate.
- 4) Assess and identify possible impediments to a successful "readjusting" or effective resolution such as the strength of the spouse relationship and other support systems (family, clergy, friends).
- 5) Stress the importance of follow-up including, but not restricted to: a full evaluation and ongoing continued contact with the family, autopsy results and genetic counseling.

In conclusion, the *Expectancy of Loss* model consists of the six themes or phases that informants described as they negotiated the experience with varying intensity of emotion beginning with the first notion of suspicion through the evaluation process and on to the waiting period before the birth of their malformed infant. For 15 of the informants, the birth and death of their babies became the culmination of the experience as they strove to acknowledge, validate and remember. It was clear that the loss experience permeated every aspect of their lives and the "thereafter" represents a new trajectory that incorporates this loss experience.

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Questionnaire vs Pedigree?

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INTRODUCTION

Obtaining the family history is one aspect of a genetic evaluation [1]. The family history may suggest a genetic concern, an inheritance pattern and/or identify other possible familial conditions.

Pedigree construction is often the method recommended and selected to review the family history [2]. This format, however, can require a considerable amount of the genetic counselor's time. A prospective study was initiated to determine if a prenatal genetic counseling questionnaire could substitute for the verbal construction of a pedigree.

METHOD AND MATERIALS

Study criteria. The following criteria were established to determine a woman's eligibility: 1) currently pregnant, 2) referred for genetic counseling for advanced maternal age only, 3) genetic counseling obtained only at the Genetics Center, 4) able to speak and read English.

Study population. Of 382 women who were referred for genetic counseling, 55 potential candidates were identified. Three women were excluded because not all criteria were met. Fifty-two participants were included in the study.

Questionnaire. Consisted of 14 questions to assess individual and family history. These are listed in Figure 1.

METHODOLOGY

Upon arrival, the participant was asked to complete the questionnaire. If her partner were present, they were requested to consider the history of both families when completing the questionnaire. If her partner were not present, the participant was requested to complete the form for both families to the best of her knowledge. No questions were answered by the counselor before or while the questionnaire was being completed.

QUESTIONNAIRE

Yes No

- ☐ ☐ 1. Will you be 35 years old or older when the baby is due?
Age when due _____
- ☐ ☐ 2. Except for marriage, are you and the baby's father related to each other (i.e. cousins)?
- ☐ ☐ 3. Have you had two or more pregnancies that ended in miscarriage or a child who died around the time of delivery?
- ☐ ☐ 4. Have you or the baby's father had a stillborn baby?
- ☐ ☐ 5. Have you or the baby's father had a child with a birth defect, genetic condition, or mental retardation?
- ☐ ☐ 6. Do you or the baby's father have a birth defect, genetic condition, or a chromosomal abnormality?
- ☐ ☐ 7. Does your family or the family of the baby's father have children with birth defects or a condition that has been diagnosed to be genetic or inherited?
- ☐ ☐ 8. Are you or the baby's father from any of the ethnic racial backgrounds listed below?
☐ Jewish ☐ Black ☐ Asian ☐ Mediterranean (Greek or Italian)
- ☐ ☐ 9. Have you or the baby's father ever been screened for any of the disorders listed below?
☐ Tay-Sachs ☐ Sickle Cell ☐ Thalassemia ☐ PKU
- If yes, results _____
- ☐ ☐ 10. Do you have any serious health problems such as insulin dependent diabetes mellitus or epilepsy?
- ☐ ☐ 11. Have you taken any drugs during this pregnancy such as seizure medications, alcohol (more than two drinks/glasses daily), anti-cancer drugs, anticoagulants (blood thinners), lithium or acutane?
If yes, list the drugs _____
- ☐ ☐ 12. Do you think you are at a greater-than-average risk to have a child with a birth defect or genetic disorder?
- ☐ ☐ 13. Do you want a maternal serum alpha fetoprotein (MSAFP) test performed?
14. Please circle highest level of education completed:
Mother 9 10 11 12 1 2 3 4+
Father 9 10 11 12 1 2 3 4+

I have answered the above questions, and to the best of my knowledge, these statements are correct.

Patient Signature	Date
-------------------	------

OPTIONS

Patient referred for further testing or counseling concerning:

--

Appointment	Referred By
-------------	-------------

Fig. 1.

A verbal history with pedigree construction was then completed by the counselor. Summary questions were then asked by the counselor to determine if there was a family history of:

Down syndrome or other chromosome abnormality;

Birth defects such as spina bifida, anencephaly, hydrocephalus, congenital heart defect, cleft lip, cleft palate, dislocated hips, clubfeet;

Infant/early childhood blindness, cataracts, glaucoma, hearing loss;

Mental retardation, slow learner, or need for special education;

Seizures;

Unusual tallness or shortness;

Consanguinity;

Cystic fibrosis or sickle cell disease (depending on race).

RESULTS

Of the 52 pedigrees completed, the pedigree-obtained information had not been identified on 32 (61.5%) of the completed questionnaires. Examples of information gained from the pedigree completion included a family history of: seizures, hemophilia, webbed fingers, scoliosis, attention deficit disorder, mental retardation, cleft palate, muscular dystrophy, stillbirths, ear deformity, "hole in back," cleft lip, congenital heart defect, hydrocephalus, pyloric stenosis.

CONCLUSION

The questionnaire can be a beneficial tool to gain information about the family history. Limitations in the current questionnaire were identified. Questions regarding more specific birth defects and the use of lay terminology may improve the questionnaire format. Retesting of a revised questionnaire may be of interest.

A detailed pedigree provides more information regarding genetic concerns than can be obtained by the simpler genetic questionnaire used in this study. Pedigree construction is an area of genetic evaluation that, in the long run, is time well spent by the genetic counselor.

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The Role of the Genetic Counselor in a Unique Preconception Substance-Use Education Program for Low-Literate Minority Women

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INTRODUCTION

Prenatal substance use (alcohol, illicit drugs and tobacco) can lead to pregnancy loss, low birthweight, infant mortality, developmental disabilities/mental retardation, birth defects and pediatric AIDS. Alcohol and drug use may have irreversible deleterious effects on the fetus in the first trimester of pregnancy, the most critical period for fetal development. However, all of these harmful effects are completely preventable through abstinence *prior* to pregnancy conception. This project demonstrates that the experience and expertise of a genetic counselor may be applied to the design and implementation of a model preconception program for low-literate minority women and professionals regarding prenatal substance use.

Many women are at risk for having a pregnancy harmed by substance use, as evidenced by recent survey data. The American Lung Association has found that 25%–30% of all pregnant women in the United States smoke cigarettes at some time during their pregnancy [1]. The Centers for Disease Control found that one-sixth of all women of childbearing age in the U.S. use enough alcohol, either chronically or episodically, to put them at risk for “fetal alcohol syndrome” or fetal alcohol effects [2]. Many more pregnancies are at risk for alcohol-related pregnancy loss. In two recent surveys, the National Association for Perinatal Addiction, Research and Education (NAPARE) has found that approximately one in ten (10–15%) of pregnant women in the U.S. use illegal substances, especially cocaine and marijuana [3, 4]. Both NAPARE studies found that the percentage of pregnant women using illegal substances was essentially the same in public and private populations. Substance use in pregnancy occurs in women of all racial, ethnic and socioeconomic backgrounds.

The potentially harmful effects of prenatal substance use are many and are entirely preventable. Cigarettes, alcohol and illegal drugs used during pregnancy may cause pregnancy loss (miscarriage and stillbirth), an increased incidence of low birthweight infants, and an increase in the infant mortality

rate. Low birthweight is the most consistent finding in liveborn infants exposed to prenatal substance use. Alcohol or polydrug use may cause central nervous system damage and birth defects. Some drug-related behaviors also increase the risk for perinatal AIDS.

PRECONCEPTION INTERVENTION

Since harm can occur so early in pregnancy it is fortunate that public health care policy is moving in the direction of preconception health, as evidenced by the publication, "Caring for our Future" released by the Public Health Service on October 2, 1989—Child Health Day. "Caring for our Future" asserts, "to ensure the health of the pregnant woman and the developing fetus, preconception care should be an integral part of prenatal care" [5]. This publication recommends that substance-using women be identified preconceptionally, and that these women receive counseling, and referrals to substance use treatment programs, smoking cessation programs, and other sources of help. Along the same public health policy lines, one of the year 2000 health objectives under current consideration is that "95% of all health care providers [not just obstetricians and gynecologists but all specialists serving women] would provide preconception counseling regarding prenatal substance abuse" [6].

BARRIERS TO CARE

Through my direct counseling of low-income minority women who have previously had a substance-abusing pregnancy, I have identified several barriers to their receiving preconception intervention. These barriers need to be considered when designing preconception education programs for this group.

- 1) Women in this group underuse traditional medical services including: gynecologic, family planning, prenatal, postpartum and well-baby care.
- 2) There is a lack of printed educational materials at appropriate readability (literacy) levels regarding prenatal substance abuse, especially ones that are culturally sensitive and include local resources.
- 3) There is a lack of professional staff knowledge of the facts regarding these agents' teratogenic effects, the impact on maternal and child health and local resources.
- 4) There is a minimal staff experience in the primary care setting with intervention strategies: identifying, counseling and referring substance-using women. Some staff, especially those serving middle class private patients, are also resistant to addressing these issues.

GENETIC COUNSELING QUALIFICATIONS

The genetic counselor's training and expertise is well suited to overcoming these barriers. Genetic counselors:

- 1) Know the health care delivery system.
- 2) Communicate technical information in simple terms (ie, have skills to develop low-literacy materials).
- 3) Know principles of teratology and the rationale for preconception programs.
- 4) Know and have access to community resources.
- 5) Are experienced with intervention strategies: identifying, counseling and referring at-risk women.

PRENATAL SUBSTANCE ABUSE EDUCATION PROGRAM (PSAEP)

The PSAEP began in July 1988 as a preconception public and professional education program. The National Capital Area chapter of the March of Dimes funds this program providing 20% of the salary for one position, travel funds, and monies for printing brochures and other educational materials. The project's goal is to decrease alcohol, illegal drug and cigarette use among women of childbearing age prior to conception in order to prevent the harmful effects of prenatal substance use. The PSAEP provides two services to overcome the aforementioned barriers: a culturally sensitive low-literacy brochure and professional education seminars.

LOW-LITERACY BROCHURE

The low-literacy brochure "I Want to Have a Healthy, Happy Baby: Important Things to Know About Drugs and Alcohol Before You Have a Baby" was written at the fourth grade level and contains basic information for women of childbearing age. The information includes answers to these questions:

- What are the harmful effects of cigarettes, alcohol, and drugs?
- What can I do to prevent harmful effects?
- What behavior changes can I make to insure having a healthy baby?
- What should I do if I am addicted?
- What help is available to me?

The brochure includes resources such as drug and alcohol treatment centers, hotlines, phone numbers for Alcoholics Anonymous (AA), Narcotics Anonymous (NA), prenatal care and a Prenatal Substances Abuse Prenatal Clinic. In the past year, 20,000 brochures have been distributed at the

following sites: junior and senior high schools, drug and alcohol treatment programs, family planning clinics, public health gynecology clinics, prenatal, adolescent and well baby clinics, hospital maternity wards and social work departments, WIC offices, social service agencies, adoption agencies and offices of prevention workers. An additional 7,000 brochures were distributed door to door to residents of low-income housing projects. In the past few months, PSAEP has also served homeless shelters and community health fairs. In the first year of operation, over 10,000 brochures were requested. The PSAEP grant allowed for the publication of 10,000 brochures. An additional 10,000 brochures were printed and distributed with funding from Georgetown University-Child Development Center, the Alcohol and Drug Abuse Services Administration (ADASA) of D.C., and the Office of Substance Abuse Prevention (OSAP). OSAP distributed approximately 2,000 copies of the brochures in the Alcohol-Related Birth Defects Awareness Week 1989 packet. In response to this effort, agencies in approximately 16 different states have requested camera-ready copies. Camera-ready prints of the PSAEP brochure are made available to agencies wishing to use this brochure in their own communities.

The low-literacy brochure was written with input from staff of literacy organizations, substance abuse counselors, public health agency workers, consumers and liberal use of the book, "Teaching Patients with Low Literacy Skills" [7]. This book is highly recommended to all genetics professionals for the design of useful educational materials.

PROFESSIONAL EDUCATION SEMINARS

The PSAEP serves professionals by offering on-site professional education seminars. In the past year and a half, approximately 50 presentations to over 800 professionals have been given at brochure distribution sites. These professionals include nurses, social workers, physicians, WIC staff, substance abuse counselors, mental retardation prevention workers, and others. The presentation, which ranges from one to three hours and averages 1½ hours, includes the following:

- 1) The impact of prenatal substance abuse on maternal and child health.
- 2) The specific effects of alcohol, cocaine, marijuana, PCP, heroin, methadone and cigarettes on pregnancy outcome and infant development.
- 3) Intervention strategies for at-risk women and infants. Approximately half of the presentation is on intervention strategies with emphasis on identifying at-risk women through history taking, counseling women with the PSAEP brochure and other educational tools, and referring alcoholic and drug-dependent women to treatment and self-help groups.

Similar intervention strategies are taught for infants. By identifying alcoholic and drug-dependent women preconceptionally we can refer them to appropriate treatment prior to pregnancy. Treatment services for *pregnant* alcoholic or drug-dependent women are currently very limited. Therefore, non-pregnant women are more likely to receive appropriate alcohol and drug treatment services. Women who use alcohol and drugs but are not chemically dependent are very amenable to preconception education and will often change their behaviors after this education.

Pre- and posttesting of professionals has revealed that not only is the general population in dire need of this education, but so is the professional community. Pre- and posttesting has revealed that approximately one third of all professionals served do not answer correctly that *preconception abstention* is the way to avoid the harmful effects of prenatal substance use.

CONCLUSION

In conclusion, there is a need for both professional and public education regarding prenatal substance use. There are barriers to low-income, low-literate minority women receiving preconception intervention regarding prenatal substance use. However, these barriers can be overcome by specially designed educational programs. Second, public health policy is moving toward preconception intervention. Preconception education has the advantage of identifying those women who use these teratogenic substances so that nonaddicted women can change behaviors prior to pregnancy conception. Women with alcohol or drug problems can be referred to appropriate treatment services *prior* to pregnancy conception. This project demonstrates that the experience and expertise of the genetic counselor may be applied to the design and implementation of a model preconception program for low-literate minority women and professionals regarding prenatal substance abuse. This program is easily replicated and may be adapted to other special populations and to other types of preconception education programs.

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The Instrumental Role of a Genetic Counselor in a Multidisciplinary Setting: The Craniofacial Team as a Model

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INTRODUCTION

The craniofacial team is a multidisciplinary group of specialists who provide coordinated health care for patients with isolated cleft lip/palate or more complex conditions with multiple congenital anomalies. The craniofacial team model illustrates the valuable role a genetic counselor plays in a multidisciplinary setting. In addition to being an instrumental member, involvement in a multidisciplinary group provides ongoing learning experiences, opportunities to teach and inform other specialists about genetic principles and conditions, and opportunities to develop joint research projects.

The multidisciplinary team approach to the evaluation of complex patients involves the gathering of many specialists during a defined clinic time span to assess patients with similar or related conditions. Such an approach to patient care has many advantages: 1) It provides a carefully coordinated, multispecialty, comprehensive approach to diagnosis and treatment. 2) It offers the convenience of seeing multiple specialists during a single visit. There is also less disruption of the family's work and school routine. 3) It facilitates communication among the many health specialists involved in each patient's care. This minimizes the number of office visits, hospital admissions and surgical procedures for each patient and, therefore, decreases duplication of effort, increases efficiency of care and expedites implementation of services. 4) It allows for growth and education of the team members and, therefore, improves quality of care provided to patients. The team also provides a fertile learning experience for trainees in many disciplines.

There are also financial advantages to the multidisciplinary approach. Cognitive genetic services have been documented to be time-consuming, labor-intensive, and not self-supporting. Genetic services often are reimbursed inconsistently, may not be authorized, or may be reimbursed at a low rate by third-party payers [1]. Increasing awareness of the genetic component of many disorders has resulted in greater demands for genetic information and assessment [2]. Provision of these services in a multidisciplinary setting

increases the likelihood of reimbursement, since insurance companies often authorize payments for assessment by the entire team. In addition, all diagnostic studies recommended by the team are often automatically authorized, avoiding long delays in scheduling further investigations.

Since multidisciplinary clinics rotate patients through numerous specialties during a finite time span, there is often limited time for patient assessment by each specialist. The genetics evaluation provides valuable information to other disciplines and patients, but a complete assessment is labor and time intensive, comprehensive, and varies in complexity with the age of the patient and type of problem. In a multidisciplinary team setting, the genetic counselor can play an important role in implementing efficient assessment.

ORGANIZATION OF THE CRANIOFACIAL CLINIC

The core craniofacial team is comprised of 12 specialties including plastic surgery, pediatrics, genetics, psychology, social services, audiology, speech pathology, nursing, orthodontics, prosthodontics, pedodontics and otolaryngology (Table 1). Ophthalmology and neurosurgery visits are scheduled as needed. The patients are rotated through specialties appropriate for age and diagnosis. Although the evaluation by each specialist may vary in length according to the needs of the patient and examiner, each has an average of 20 minutes per patient. The genetics visit generally requires an average of 30 minutes per patient. All patients seen during clinic are discussed at the clinic conference. Each specialist reviews his/her findings and recommendations, resulting in a team approach to patient care and management. A clinic summary report is generated, including team recommendations for further testing and follow-up. Each specialist is responsible for making arrangements for the tests he/she has recommended.

THE ROLE OF THE GENETIC COUNSELOR

An important aspect of the genetic counselor's role is completed prior to the craniofacial clinic. A clinic schedule is received three to seven days before clinic allowing the counselor to review patient records. A telephone intake including a detailed family, pregnancy, and developmental history is obtained prior to the appointment. We have developed a form which allows this to be easily accomplished. Parents receive an explanation of the clinic visit and purpose of the genetics evaluation and are encouraged to formulate questions for discussion.

At the beginning of each clinic, the patient care is prioritized with "new" patients seen first, especially those who live a long distance away (Table 2). Patients whose evaluation is expected to be more lengthy due to complexity

TABLE 1. Members of the Craniofacial Team

Plastic Surgery <ul style="list-style-type: none"> ● Out-patient cleft lip repair ● Advanced and innovative surgical techniques in cleft palate repair ● Full spectrum of maxillofacial, craniofacial and orthognathic surgery ● Three dimensional imaging for treatment planning ● Surgery to correct external ear deformities, including microtia 	Other Hospital Resources <ul style="list-style-type: none"> ● Pediatric anesthesia ● Neonatal and pediatric intensive care units ● Physical therapy/occupational therapy ● Pediatric rehabilitation unit
Pediatric Dental Services <ul style="list-style-type: none"> ● Infant feeding obturators ● Premaxillary orthopedics ● Early interceptive orthodontics to minimize later problems ● Conventional orthodontics, functional appliances, and lingual ("invisible") braces ● Orthodontic planning and treatment for orthognathic surgery ● Speech aids, crown and bridge services, cosmetic dentistry, and facial prosthetics 	Neurosurgery <ul style="list-style-type: none"> ● Stereotactic surgery ● Craniosynostosis and craniofacial reconstruction ● Treatment of hydrocephalus
Genetics <ul style="list-style-type: none"> ● Dysmorphology: triage, full evaluation, and syndrome identification ● Comprehensive genetic counseling ● Prenatal diagnostic evaluation: ultrasound, amniocentesis, and chorionic villus sampling ● Long-term coordination of care/nonteam services for complex patients 	Audiology and Speech Pathology <ul style="list-style-type: none"> ● Pediatric hearing evaluation individualized by age and ability to cooperate ● Impedance testing ● Speech and language assessment ● Speech therapy
Psychologic and Social Services <ul style="list-style-type: none"> ● Psychologic testing appropriate for age ● Short-term psychologic counseling for children and parents ● School intervention to promote positive social interaction ● Patient and family support groups and social activities ● Cosmetic and style consultations to enhance self-image 	Otolaryngology <ul style="list-style-type: none"> ● Treatment of chronic otitis media ● Diagnostic evaluation and treatment of laryngeal and airway problems ● Pediatric cochlear implants ● Endoscopic sinus surgery
	Pediatrics/Adolescent Medicine <ul style="list-style-type: none"> ● Coordination of care for patients with complex medical, psychosocial and developmental needs ● Liaison with primary care providers outside of the hospital ● Full pediatric specialty services including cardiology, pulmonary medicine, neurology, gastroenterology
	Ophthalmology <ul style="list-style-type: none"> ● Strabismus, ptosis, and tear duct surgery ● Neuro-ophthalmology ● Ocular-genetics ● Ocular-oncology
	Nursing <ul style="list-style-type: none"> ● Feeding evaluation and therapy ● Growth and development monitoring ● Patient and parent teaching

TABLE 2. Prioritization of Patients

		New Patients	Return Patients
High Priority	Routine:	Isolated CL/CP; microtia; Facial-Auricular-Vertebral Sequence (FAV); young adult patients who are graduating from team follow-up	
		Patients who are geographically distant have greater priority than those who live in close proximity	Complex: Annual follow-up evaluation
	Complex:	Triage and defer for complete initial evaluation in genetics clinic. Follow-up visits are coordinated either in craniofacial clinic or separately in genetics clinic	
	TRIAGE		
	Routine:	Non-English speaking patients are deferred for "special language" genetics clinics	
			Routine: No follow-up unless family has questions, new medical information has developed, pregnancy, or proband is old enough for individual counseling
Low priority			

and/or language barrier are triaged and given an appointment for a genetic evaluation separate from the craniofacial team visit, allowing time for a proper evaluation.

Since each specialist is given a limited amount of time per patient, the assessment of each patient is conducted efficiently. During clinic, patients are seen in rotation with the medical geneticist. The counselor may also assist by noting the verbal descriptions and measurements obtained by the medical geneticist during the physical exam. Parents and older patients are counseled by the genetic counselor. Counseling includes information on incidence, embryologic timing, recurrence risk and available prenatal testing, if appropri-

ate. The medical geneticist reviews pertinent physical findings or associated medical concerns.

Following clinic, the team members assemble for case conference to discuss an approach to treatment and management of each patient. The genetic counselor then coordinates tests ordered for diagnosis and management, tracks lab results, reviews results with the medical geneticist, informs parents of the findings as appropriate, and arranges any additional recommended tests or follow-up appointments. The counselor also coordinates the specialty genetics clinic comprised of the complex/non-English speaking patients.

BENEFITS OF OUR APPROACH TO THE GENETICS ASSESSMENT IN THE CRANIOFACIAL CLINIC

Genetics is an integral part of the craniofacial team. The genetics assessment provides and/or confirms the patient's diagnosis so that accurate information regarding etiology, prognosis and recurrence risks can be given to the patient and team members. An accurate diagnosis is especially important prior to surgeries if there is an increased risk for surgical complications, and in situations where pregnancy is planned or ongoing.

The involvement of the genetic counselor enables genetics to participate in a significant manner by allowing a greater number of patients to be seen during a short period of time. This has been of value especially with the significant and continued growth of the craniofacial team (Fig. 1). The genetics evaluation can also be performed without monopolization of the patient in a team setting.

Discussion with families revealed that the telephone intake obtained by the counselor prior to the day of clinic has been helpful in many ways.

- 1) It serves as a reminder of the clinic appointment and, therefore, decreases the likelihood of missed appointments.
- 2) It establishes rapport with the family and alleviates some patient anxiety regarding the clinic visit.
- 3) It allows us to encourage patients to ask questions on the day of their appointment.
- 4) It gives the patients an understanding of what to expect on the day of their clinic appointment.
- 5) It prompts parents to verify additional history or family data prior to the visit.

The intake has been helpful also in identifying special concerns, social problems and areas requiring attention (eg, prenatal medication exposure can be researched prior to the clinic; other team members can be alerted to issues of concern). We have also learned through a preliminary survey, conducted following team visits, that some of the parents' most important questions on the day of the clinic include those regarding etiology and recurrence. Of those

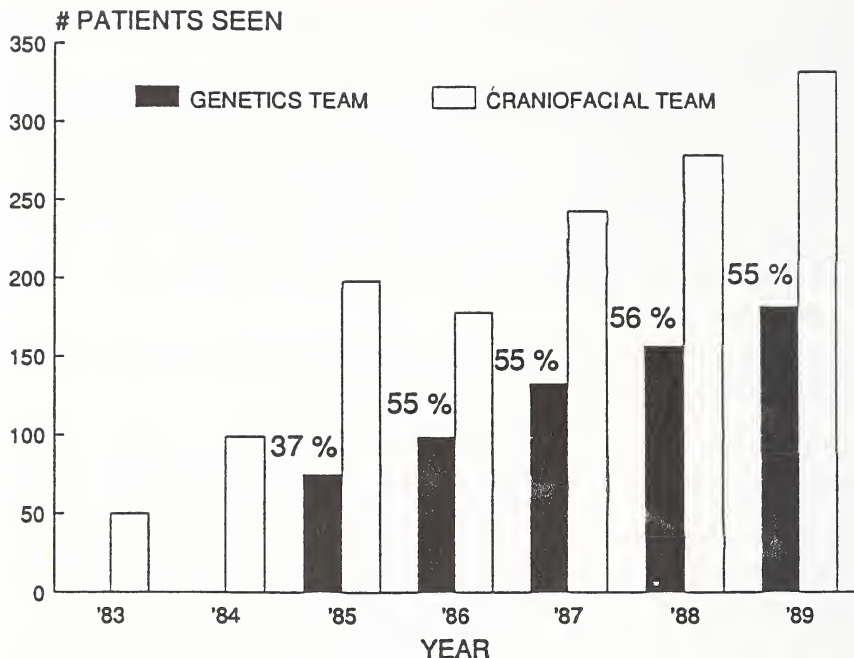


Fig. 1. Not all patients scheduled are appropriate for the genetics staff to see. In 1985, the medical geneticist saw approximately 37% of all patients. A genetic counselor was added to the team in 1986. Over the last four years (1986–1989) an average of 55% of all patients have been evaluated, even with the continued growth in patient load.

parents surveyed, the genetics evaluation was rated an average of 9, on a scale of 1–10, with 10 being most helpful. The involvement of genetics in the craniofacial team also provides team members with ongoing learning experiences, and fosters development of joint research projects.

CONCLUSION

The genetic counselor can play an important role in a multidisciplinary team setting, providing valuable information to both the team and the patient, and allows efficient assessment without disruption of the patient's evaluation by other specialists.

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Teratogen Exposures to Health Care Workers

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Health care facilities present workers with a wide variety of potential health and safety hazards. Many of the concerns regarding these exposures involve adverse reproductive effects. These may include menstrual disorders, infertility, reduced libido or impotence, miscarriage, stillbirth, obstetrical complications, premature delivery, fetal growth retardation, congenital abnormalities, mental retardation, and childhood cancer; in some cases males as well as females may be at increased risk.

There are an estimated 8 million health care workers in the United States. Types of employees include maintenance workers, housekeepers, nurses and aides, physicians and medical students, radiology technicians, dental assistants, operating room staff, pharmacists, medical technologists, respiratory therapists, and administrative staff.

Housekeepers and laundry staff, for example, may be exposed to potentially dangerous chemicals (cleaners, disinfectants, sterilizing agents, solvents), infections (hepatitis), and physical stress. Nurses are exposed to a myriad of agents including medications (anti-neoplastic, aerosolized anti-virals), infectious organisms (hepatitis, CMV, herpes zoster, rubella), anesthesia gases, as well as x-rays and radioactive isotopes. Pharmacists are often exposed to anti-neoplastic agents, and laboratory personnel are exposed to a variety of chemicals and solvents as well as infectious agents. Administrative staff report concerns about exposures to VDTs. Most personnel work long hours and do a physically and emotionally stressful job.

The genetic counselor/nurse geneticist who has a health care worker as a client should be aware of these potential reproductive risks. In some cases there are strategies that can reduce the risk or help avoid the exposure. For example, vaccinations against rubella or hepatitis B can be recommended for the non-immune, non-pregnant woman. Use of gloves, gown, mask and/or goggles may help avoid risk to certain chemicals, medications, and organisms. If the exposure has already occurred, it is important to have accurate data regarding the potential risk (or *lack* of risk) engendered. Knowledge of pertinent resources is also important; the National Institute for Occupational Safety and Health, for example, has exposure standards for a variety of common hospital chemicals [1-5].

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Ribavirin Aerosol Administration and Potential Environmental Exposure to Females of Childbearing Age

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Ribavirin is an FDA approved antiviral agent for treatment of respiratory syncytial virus. It is administered by aerosol through a head hood, mist mask, or oxygen tent. Because these methods are not closed systems, the aerosol escapes into the environment where it can be inhaled by any persons who are in the room. Laboratory testing indicates that ribavirin is teratogenic in most animals. Currently, there are no reports that link ribavirin to human teratogenesis or fetal loss. This descriptive study was undertaken to determine the nature and prevalence of ribavirin aerosol administration in pediatric hospitals and to ascertain the extent of potential environmental exposure to females of childbearing age. The researcher-developed tool used was a pretested self-administered questionnaire. The questionnaire, along with a self-addressed stamped envelope and postcard for follow-up, and instructions, were mailed to nurse administrators of the 91 U.S. pediatric hospitals listed by the National Association of Children's Hospitals and Related Institutions (NACHRI). From the 63% of questionnaires returned, the median age of female hospital employees was 29.5 years. Ribavirin was administered in 79.4% of the responding hospitals ($N = 63$). The head hood was used in 82% of the hospitals with 60% indicating they preferred or only used this method to deliver aerosolized ribavirin. Only one head hood was used in previous environmental studies evaluating ribavirin exposure to health care workers. Ventilators, essentially closed systems of delivery, were the primary source of exposure in the environmental studies. In this study, only 6% of the respondents indicated that a ventilator was the preferred or only method used for ribavirin aerosol delivery. Sixty-six percent of the hospitals had written policies or procedures that warned pregnant personnel from providing direct care to children receiving ribavirin. Only 42% of women at risk for pregnancy were advised in the same manner. Thirty-two percent of the respondents indicated they have written guidelines that include the necessity of informing female visitors of childbearing age that ribavirin is a potential reproductive hazard. The results of this study suggest there are a significant number of females at risk for being exposed to ribavirin during a period when they are

most vulnerable to spontaneous abortions or embryonic malformations. This information needs to be used to plan environmental studies which survey female employees' ribavirin exposure and absorption in a typical work setting using preferred methods of delivery.

Preconceptional Family Health Evaluation: Bringing Clinical Genetics Education To New England Family Planning Patients

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INTRODUCTION

A six-state network of professional researchers, policy makers and practitioners has extended new developments in genetics to family planning centers. Sponsored by the New England Regional Genetics Group (NERGG), genetics clinicians, state health planners, family planning staff, medical anthropologists and patients are designing a program to improve clients' knowledge of personal and reproductive genetic risks. Patient and professional ethnographic interviews are a critical component of this study, as its greatest challenge is the successful linkage of organizational structure with respect for individual and reproductive freedoms. The program is entitled "Family Health Evaluation Program" to emphasize the family aspect of genetic services and to dispel any association with eugenics.

The Family Health Evaluation's objectives and goals are to increase access to medical genetics services by underserved populations, specifically family planning patients. It provides a voluntary opportunity for family planning patients to learn about their own family health histories and potentially increase their reproductive options. It also provides continuing education for family planning staff and assistance in determining medical genetics services needs in New England communities as it expands on previous work done in New York, Wisconsin, Texas, Pennsylvania and West Virginia.

The definition of genetic counseling from the Committee on Genetic Counseling, American Society of Human Genetics [1] has been used as an introduction for family planning participants. Planned Parenthood annual reports and other family planning literature have been used as introductory materials for project staff. This project is interdisciplinary, requiring awareness of all participants' cultural systems, theories, models and beliefs. This paper presents the interweaving of the goals of the four component groups: medical genetics, family planning, health policy planning and medical anthropology.

Access to genetic counseling has been reported as less than acceptable for the USA population and at least part of the Canadian population, especially among lower socioeconomic, minority or unmarried women [2]. Each country embodies the dichotomy present in most industrialized nations; wealth in the midst of poverty and a differential in access to certain aspects of life. Pooled data from 19 countries studied by Gardiner et al [2] resulted in the following percentages of those countries reporting access to medical genetics services as less than acceptable for the following populations: 1) rural (66%); 2) women (33%), and 3) lower socioeconomic group members (22%). Through implementation of a simple, efficient voluntary self-administered tool designed to assess genetic risk in family planning patients, the Family Health Evaluation Program helps by bringing less accessible genetic education and counseling into the family planning model.

Figure 1 shows the interaction of the main project institutions with NERGG and the clients, and enumerates the ethnic groups utilizing family planning clinics in New England.

The Family Health Evaluation Program is based on past studies conducted in a variety of settings, but is unique in its attempt to implement this concept in a multistate region. The hypothesis for all these studies has been: implementing a tool to screen for genetic/birth defect risk in family planning clinics,

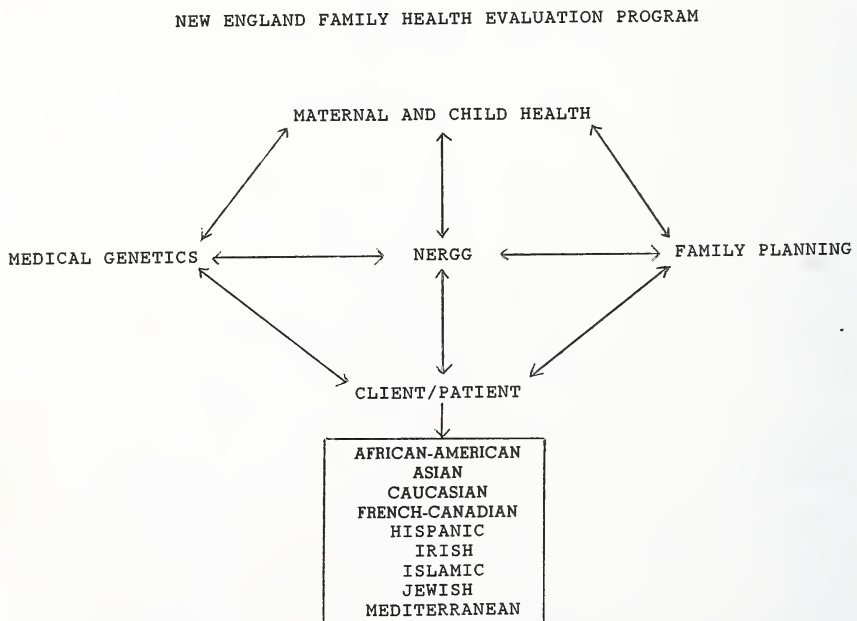


Fig. 1.

will improve access to genetic counseling for family planning patients. Since there is no reliable quantitative baseline with which to compare results for this part of the project, this report represents an educational project whose greatest value lies in the process of communication and implementation.

METHODOLOGY

Background Studies Linking Family Planning and Genetic Counseling

Family planning services offer valuable education to families, some of whom may never be identified without obtaining specific medical and family history.

In 1980, a genetic screening questionnaire was developed. This two-part questionnaire, which became known as the Genetic Risk Scoring Instrument (GRSI), was partially supported by the Planned Parenthood Federation of America [3]. It proved to be an easily administered genetic risk assessment tool, which provided a voluntary and completely confidential service to family planning patients. It was piloted at Planned Parenthood clinics in Wisconsin, Texas and New York with evaluations that confirmed patients' comprehension of both the English and reading level used. Patients were asked questions before piloting began, which confirmed their interest in such a program. Language was not noted as a barrier at any of the original clinics.

Because family planning clinics have differing procedures and employ personnel with varying medical backgrounds, it was necessary for the GRSI to be efficient and adaptable. A "risk-scoring grid" was developed that provided family planning health professionals clear guidelines for offering appropriate information, recommendations or referrals. The grid also significantly expanded the amount of information obtained in the patient's family/medical history. In addition, the Wisconsin site reported that the GRSI helped demonstrate the need for medical genetics services in their community and led to the subsequent opening of a genetics clinic.

Sites participating in the GRSI reported that some patients chose to delay obtaining genetic counseling services for up to five years after completing the instrument. Eventual return to a genetics clinic for further information was usually preceded by a desire to become pregnant.

A more recent modification of the GRSI was studied in Pennsylvania under a Maternal and Child Health (MCH) Special Project of Regional and National Significance (SPRANS) grant in the Mid-Atlantic Regional Human Genetics Network (personal communication, Brandt, 1988). The SPRANS experience resulted in almost statewide implementation of the GRSI concept. The Pennsylvania Department of Health and genetics personnel devised a core list of elements for all instruments used in family planning clinics. Implementation, follow-up and continuing inservices for family plan-

ning liaison staff (usually RNs or nurse practitioners) are successfully in place.

IMPLEMENTATION

Continuing education proved successful in the Pennsylvania program only when a 40-hour training program, conducted over one to two months, was provided. This program has successfully negotiated crucial Medical Assistance (Medicaid) coverage to reimburse for liaison staff time at \$7.00 per participating patient. Monies to support program continuation have largely come from the Pennsylvania MCH block grant. Other prenatal (versus preconceptual) risk assessment tools have been reported in the literature. Blattner et al [4] found such a program to be an "effective anticipatory alert device to identify women at risk for congenital and genetic defects, and for increased staff awareness of these types of problems in pregnancy." Bach et al [5] found their genetic screening questionnaire "more effective in eliciting a genetic and teratogenic history than the current method used by the family practice physicians."

NEW ENGLAND REGIONAL GENETICS GROUP GRANT

During 1987, NERGG encouraged members interested in a preconceptional, self-administered voluntary program for assessing genetics/birth defects risk among family planning patients to submit a grant developing such a program. This was funded as a two-year study [6] with Year I including state site visits to: 1) determine feasibility of implementing such a program in each state; 2) develop the risk assessment tool; 3) design the training program for family planning staff; 4) develop data collection; and 5) develop evaluation materials.

Figure 2 depicts communication for the NERGG grant among genetics clinicians, family planning organizations, public health policy planners and medical anthropologists. The areas of influence within this communication will vary from region to region around the country. (eg, Although NERGG has implemented projects regionally, MCH (Title V), NERGG's funding source, and Family Planning (Title X) in New England (Region One) do not issue regional programming directives for agencies they fund. Instead, they respond to grants submitted from their state and local grantees.) Because of Region One's policy, considerable grass roots efforts are needed, which may be a crucial investment for the long-term maintenance and benefits of the Family Health Evaluation Program.

Year II will involve training family planning staff followed by implementation in pilot sites. Evaluation will be followed by alterations, and results will be

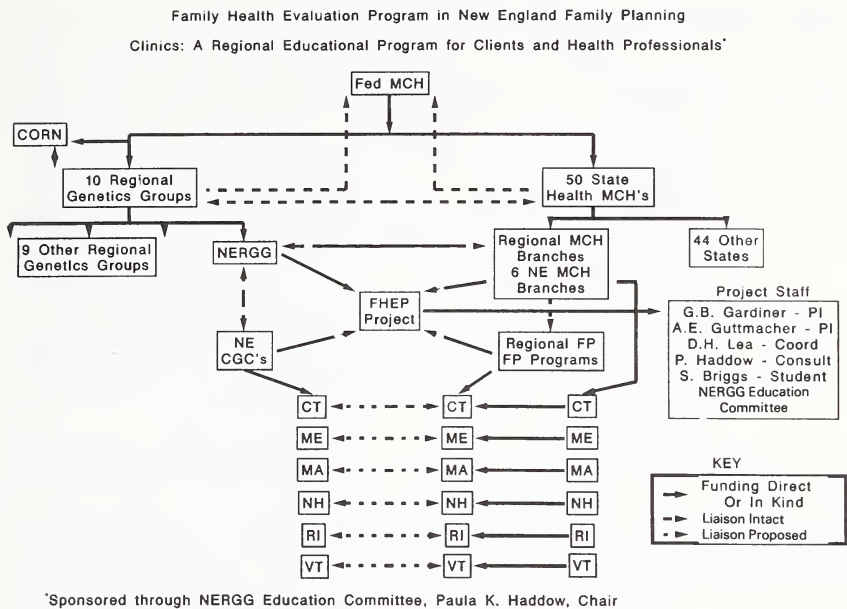


Fig. 2.

disseminated to the NERGG membership, family planning organizations, State MCH Divisions, medical anthropologists and other interstate regional genetics groups as a potential model for wider distribution.

As part of the site visits, genetic counseling education includes discussion of prenatal diagnostic options, ie, chorionic villus sampling and management options, adoption and foster care. Some family planning staff are pleased to learn that there are alternatives to therapeutic abortion in the second trimester, as they are sensitive to how difficult this option might be for some patients.

RESULTS

Table 1 lists results of the family planning state site visits. Currently, New Hampshire and Vermont are strongly considering the Family Health Evaluation Program.

To underscore the importance of the site visits and dialog with potential pilot site staff, the following is a summary of an ethnography conducted during the Maine site visit.

This visit was conducted in December 1988 in a town in Maine, population, 20,000. The largest ethnic group was French-Canadian. Sixty-five percent of the clientele were at 150% of poverty level, as determined by the Maine

TABLE 1. Pilot Site Participation Decisions

	Possible	Yes	No—At This Time
CT	Danielson*	X	
	Enfield*	X	
	Shelton*	X	
	Hartford*		X—Project size logistics
	New Britain		X—New clinic manager
	New Haven		X—Implementing services for men now
	Hispanic Health Council*		X—Lack of interpreter, short staffed
ME	Augusta	X	
	Lewiston		X—Staffing changes
MA	Hyannis		X—State Title X budget cut in half
	Falmouth		X—Short staffed
NH	West Lebanon*		—Decision pending
VT	Rutland*		—Decision pending
RI	Providence*		X—State legislation on AIDS education preempted
TOTAL		4-6	

*Planned Parenthood Clinic

Medicaid guidelines. (This is identified as one of the more wealthy areas in rural Maine.) The clinic was clean, organized and had a comfortable friendly atmosphere. Furnishings were simple but well-maintained. This clinic shared a house near the center of town with an alcohol-rehabilitation counseling agency and the Women, Infants and Children's (WIC) program. Staff consisted of a director, two nurse practitioners, a community educator, four counselors, two receptionists and a secretary.

As part of site visits, staff ethnographic interviews were conducted with clinic directors, two nurse practitioners, three counselors, and patients. The staff agreed with the program's concept, although time allotment was the main concern. Staff and patients appreciated being involved at the beginning, having the project staff respect their input and exhibit sensitivity to their environment. Although the concept of the Family Health Evaluation Program fit in with the overall goal of offering "complete and accurate reproductive health choices to all patients," staff was assured that no one expected this project to ever be their first priority. Suggestions regarding tool format, timing of offering to patients (new vs return, or annual, visits) and duplication of Family Health Evaluation Program elements by other items on family planning intake forms were made by family planning staff.

The patient interviews were scheduled at the end of their visits. The medical anthropologist was able to talk with only one patient, who indicated that if she were determined to be at risk for a genetic condition, even though she was not

planning to have children immediately, she would "go to the library to look it up."

Most family planning workers were receptive to the opportunity to gain new knowledge. Some practitioners expressed interest in attending a training session regardless of continuing education credits.

Second trimester abortion was a concern for most staff because of the physical and emotional sequelae they have observed in patients. They all expressed pro-choice positions, however, and all were committed to non-directive counseling.

Data are collected centrally for all Title V-funded family planning clinics and each clinic has both a mandatory and flexible component to their data base. This has allowed for efficient data compilation at individual pilot sites and regionally.

DISCUSSION

The Family Health Evaluation Program is currently in its first of two years. State site visits, establishment of pilot sites, interviews of patients and production of training materials have occurred. We have been successful in interesting Family Planning clinics in adding this new service.

Additional dissemination of this concept has resulted from unexpected sources. The project was presented at the North Eastern Anthropological Association meeting in Montreal in March of 1989. The curator of the National Health and Science Museum expressed interest in including the Family Health Evaluation Program risk assessment instrument in the Museum's 1991 exhibit on Human Reproduction, Growth and Development. This exhibit will be concurrent with the International Congress of Human Genetics. Interest has also been expressed by a New York State public school curriculum, *Growing Healthy*. Planned Parenthood of Connecticut revised their follow-up for their current intake form as a result of this program. Although their staff ask questions about sexually transmitted diseases (STDs) and rubella as part of their present intake form (and therefore not on the Family Health Evaluation Program form), they realized that they were not properly addressing these preconceptional fetal risks with their patients. This realization led them to order pamphlets on STDs and rubella which do address these concerns. They will offer these pamphlets to all their patients in 26 clinics throughout Connecticut.

CONCLUSION

We anticipate that the regional approach represented by the Family Health Evaluation Program will be successful in linking family planning patients to

genetic counseling services in each of the states participating at this time (Connecticut, Maine and probably Vermont and New Hampshire). This link is occurring at differing rates around the region, depending on individual family planning clinic economic and political climate. Once site visits are conducted, training is complete and implementation with patients begins, cultural issues may take on greater significance.

We predict that a woman will act responsibly for herself and her future family if it is not in conflict with positive self-esteem, as defined by personal culture in one's own environment. This project represents opportunities to: 1) increase access to medical genetics services preconceptionally for an underserved population, and 2) overcome ethnocultural barriers, both of which serve the common goal of family planning and genetics to improve education regarding personal and reproductive risks and options.

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Increased Public Awareness of Human Genetics Through Lead Teacher Training*

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The Teacher Training Program was developed in response to the frequent requests we received from various schools to give genetic lectures to students. Staffing limitations and successful one-day genetics workshops led us to develop a longer program encouraging teachers to become leaders in their school districts and train their peers.

Over the past two years, 118 elementary, middle, and senior high school "lead" teachers in two geographically diverse areas were trained in the use of genetics education materials through 5-day initial workshops and 2-day follow-up workshops approximately 6 months later.

One group of 40 lead teachers with approximately 2600 students has shown a sixfold overall increase in their teaching of clinical/human genetic principles and issues. This was accompanied by a doubling of basic background mendelian genetics or plant/animal genetics. The largest increase was among elementary school teachers (22-fold increase in hours teaching), followed by middle school teachers (sevenfold increase), and senior high teachers (sixfold increase).

After the training at workshops and classroom experiences, the lead teachers each demonstrated genetic materials to at least ten of their peers. This increased human genetics teaching to thousands of additional students. Curricula, videotapes, computer programs, books and hands-on materials relevant to the teaching of human genetics were used by the combined efforts of over 50 professionals and "master" teachers in the workshops. Teachers were from public schools, parochial schools, a school for the deaf, a school for the blind, and the home school setting.

Incentives to participate included 4 hours of graduate credit, free teaching materials, a stipend, subsistence, and substitute teacher payment. Teachers who participated in the program increased their knowledge of human genetics and the implications of new genetic technology. They had increased confidence in teaching human genetics and related issues, and changed their teaching emphasis from plant/animal genetics to human genetics. They also

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found many other subject areas into which they could integrate human genetics (math, history, social studies, human development, psychology, etc).

Our experience has shown teachers to be a highly motivated, enthusiastic, and appreciative group for educational efforts. An increased genetic literacy among our patient population is anticipated.

Attitudes Toward the Collection of Medical/Genetic Information in the Adoptive Process

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INTRODUCTION

It is estimated that 2 to 4% of the population in North America is in an adoptive kinship. In the medical genetics community four areas of concern regarding adoption have emerged: 1) adopted children who are products of a consanguineous mating, 2) the identification of a genetic problem that has medical implications for an adoptee or his/her biologic parent, 3) family histories that include psychiatric illness and/or alcohol/drug addiction, and 4) the importance of adjustment/self-identity in accessing ethnic/medical information [1].

Genetic counselors are aware of the frustration of adoptive parents and adoptees resigned to the unavailability of medical/genetic histories. Thus, genetic counselors look to the adoption field to address this issue.

Historically, a policy decreasing the emphasis on data collection was instituted to minimize the stigma of illegitimacy, protect confidentiality and promote bonding between adoptive parent and adopted child. Since the mid-1960s, there has been a greater demand from adoptees for improved access to information. Presently there are no national guidelines for collection of medical/genetic data. Further, there continue to be conflicting perceptions of the availability of information. Determining attitudinal change may assist in impacting present-day policies and practices.

METHOD

Questionnaires were collected from adoption caseworkers, adoptive parents, potential adoptive parents, and adoptees in Upstate New York from January 1988 to September 1989. This paper focuses on responses from adoption caseworkers and adoptive/prospective adoptive parents.

Survey instruments were distributed to all adoption agencies in Upstate New York including social service agencies in each county as well as private agencies. Sixty-eight (68) caseworker questionnaires were returned. Fifty additional questionnaires were distributed to adoptive parents and prospective

TABLE 1.

Parents—"How much medical/genetic information do you believe that you will receive concerning?"

Caseworkers—"How much medical/genetic information do you provide the adoptive family about?"

Figures Are Percentages of Respondents

	(1) All Info		(2) Most Info		(3) Some Info		(4) Little Info		(5) No Info	
Adopted child	13	97	20	3	40	—	18	—	9	—
Biologic mother	5	76	18	18	33	6	30	—	14	—
Biologic father	5	76	11	18	33	6	30	—	21	—
Biologic sibs	5	66	2	21	27	10	27	1	30	1
Biologic grandparents	5	66	2	16	16	10	27	4	50	4
Other biologic relatives	2	63	2	16	7	9	30	3	59	9

adoptive parents who were identified through various adoption agency support groups and several workshops on adoption. A total of 45 completed questionnaires are included in this study.

The survey instrument consists of 11 questions exploring practices, perceptions and attitudes toward collection of information. This study did not evaluate how and what information is routinely collected by the adoption agency.

RESULTS AND DISCUSSION

- 1) The majority of caseworkers report that they provide all or most information they collect. Parents perceive that they are likely to receive only some or little information for first-degree relatives and no informa-

TABLE 2.

Parents—"How do you rate the importance of the following information about your adopted child?"

Caseworkers—"How would you rate the importance of the following information about the biologic parents to the adopted child?"

Figures Are Percentages of Respondents

	(1) Most Important		(2) Very Important		(3) Important		(4) Somewhat Important		(5) Least Important		(6) Not Applicable	
Location of birth	2	12	7	24	22	26	31	24	36	10	2	4
Education	—	13	11	28	25	43	23	15	11	1	30	—
Ethnic background	4	41	22	31	27	21	29	7	18	—	—	—
Health/medical	63	81	27	15	4	4	4	—	—	—	2	—
Occupation	—	12	5	21	7	36	25	24	18	6	45	1
Physical appearance	—	34	11	26	29	21	42	19	18	—	—	—
Religion	6	12	13	22	26	32	29	18	23	16	3	—

TABLE 3.

Parents—"How do you think that your adopted child might rate the importance of the following information?"

Caseworkers—"What importance do you believe an adopted child might place on the items listed below?"

Figures are Percentages of Respondents

	(1) Most Important		(2) Very Important		(3) Important		(4) Somewhat Important		(5) Least Important		(6) Not Applicable	
Location of birth	9	32	31	34	40	18	18	9	2	6	—	1
Education	2	16	19	38	19	32	31	13	7	1	22	—
Ethnic background	20	47	40	40	22	13	13	—	5	—	—	—
Health/medical	27	59	23	27	32	13	16	1	—	—	2	—
Occupation	5	16	19	34	12	36	22	13	5	1	37	—
Physical appearance	21	49	28	34	30	16	14	1	—	—	7	—
Religion	7	15	12	22	29	27	29	29	18	7	5	—

tion for second-degree relatives (Table 1). Eighty-eight percent of caseworkers report that providing medical/genetic information is an agency policy.

- 2) Caseworkers tend to value information in all areas more than the adoptive parent or prospective adoptive parent. Professional experience of caseworkers spanned 1–45 years, whereas the parent experience in the adoptive parenting process was limited to 12 years. Feigelman and Silverman's 1986 longitudinal study [2] focused on adoptive parents' receptiveness to open records. In 1975, their survey found that most parents agreed to learning about and making contact with birth parents. The follow-up study in 1981 indicated that adoptive parents were even more receptive to receiving new information. It appears that attitudes of adoptive parents became more receptive over time to receiving information—a change consistent with other research regarding attitude forma-

TABLE 4.

Parents—"If my child develops a serious disease or health-related condition, I would feel comfortable sharing this information with the biologic parents."

Caseworkers—"Should an adopted child develop a serious disease or health-related condition, adoptive parents are comfortable sharing with adoption agency and/or biologic parents."

Figures Are Percentages of Respondents

	Parents	Caseworkers
Strongly disagree	10	3
Moderately disagree	10	11
Slightly disagree	2	13
Slightly agree	21	11
Moderately agree	33	53
Strongly agree	24	9

TABLE 5.

Parents—"If my adopted child's biologic parent or sib develops a serious disease or health-related condition, I would be receptive to receiving this information."

Caseworkers—"Should a biologic parent of an adopted child develop a serious disease or health-related condition, the adoptive parents are comfortable receiving such information."

Figures Are Percentages of Respondents

	Parents	Caseworkers
Strongly disagree	—	6
Moderately disagree	2	6
Slightly disagree	—	11
Slightly agree	18	6
Moderately agree	30	43
Strongly agree	50	28

tion [3-5]. Caseworkers may be more aware of adoptive parents' and adoptees' evolving need for information. The single category of medical/genetic information was most significant to the newly adoptive parent with little or no value placed on the other categories (Tables 2 and 3).

- 3) The adoptive parent is perceived by caseworkers as being more comfortable in sharing important health information. However, adoptive parents did not concur (Table 4).
- 4) Adoptive parents are perceived by caseworkers as not being open to receiving information. Adoptive parents' first choice for information was the adoptive agency (Tables 5 and 6).

CONCLUSION

This study suggests that there are disparities in perception between caseworkers and adoptive parents. The genetic counselor needs to encourage the adoptive parent, or adoptee, to return to the adoption agency for access to

TABLE 6.

Parents—"If you needed medical information in regard to your adopted child, in what order would you go to the following groups to obtain that information?"

Caseworkers—"If an adoptive parent required medical information regarding their adopted child, whom should they contact?"

Figures Are Percentages of Respondents

	Adoption Registry		Agency		Biologic Family		Lawyers		Search Organization	
First choice	6	13	80	78	9	4	5	3	—	2
Second choice	49	46	11	20	29	15	8	16	3	3
Third choice	31	22	—	3	13	18	1	23	40	34
Fourth choice	6	10	3	2	13	20	34	30	44	38
Fifth choice	3	7	—	—	46	45	35	27	16	21

additional information. Finally, genetic counselors need to continue to advocate for the collection of medical/genetic histories of all family members, including first- and second-degree relatives.

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Current Status of Prenatal Diagnosis by DNA Analysis

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This paper will address gene diagnosis, or how we detect particular disease genes in individuals. Most of the prenatal diagnoses done today are carried out after chorionic villus sampling (CVS). Our laboratory started doing gene diagnosis in 1979, when Corinne Boehm joined us. Since 1979 we have performed diagnostic work in a variety of disorders, including alpha-thalassemia, beta-thalassemia, sickle cell anemia, other hemoglobinopathies, hemophilia A, and Duchenne muscular dystrophy. We also test for cystic fibrosis, Huntington disease, and hemophilia B and have begun doing gene diagnosis for neurofibromatosis.

We studied approximately 450 families in 1988, and a comparable number in 1989. Among over 2500 families studied since 1979, we are aware of two errors in diagnosis. In 1983, an error in sickle cell anemia diagnosis occurred in which a fetus was diagnosed as normal but was actually affected. The error resulted from a probe contamination in the assay. We also had a sample mix up, involving the diagnosis of hemophilia A about a year ago, where the amniocentesis was done in Massachusetts.

In terms of DNA analysis, there are two general ways to approach the problem. By several methods, we are often able to directly detect the mutation that causes the disorder. Usually when a probe is available for a particular disease, one is able to do prenatal diagnoses using indirect detection on the mutation via linkage with DNA polymorphisms. We are always working toward moving from indirect detection to direct detection of the disease-producing mutation for all single gene disorders. Many disorders have moved to the direct detection mode, which is remarkable considering how little could be done just ten years ago.

DIRECT DETECTION: SICKLE CELL ANEMIA

Let us start out with a simple diagnosis using direct detection. Sickle cell anemia is a disorder due to a single nucleotide substitution ($A \rightarrow T$) in the 6th codon of the beta globin gene. This substitution can be detected because it alters a Cvn I or Mst II recognition sequence, where the recognition sequence of the restriction enzyme is CCTNAGG. The beta-A globin is cut by this enzyme because it has that recognition sequence at this particular point. The

beta-S gene is not cut by the enzyme because of the A to T substitution. Now, it turns out that this change makes sickle cell disease a relatively simple disorder to detect. One could detect it by Southern blotting back in 1982, so direct DNA testing has been available for a long time.

The polymerase chain reaction (PCR) came into use in 1987 as a method to amplify rapidly a specific DNA sequence up to about 10-million fold in three hours. All one needs to know is the specific sequence that one is interested in amplifying; then primers are made and this kind of amplification procedure can be done. This process is what now has made prenatal diagnosis of sickle cell anemia and other disorders easier and more rapid.

In PCR, a very tiny amount of DNA, or about 1/3,000,000 of the sample, becomes half the DNA in the solution after three hours. So for the beta-globin gene, we can make primers to amplify the key region in this very small gene. After amplification with these primers, and electrophoresis of the DNA, we detect a very strong single band of the particular, specifically amplified DNA. Primers that are 750 base pairs apart generate a very intense band of 750 base pairs, demonstrating specific amplification of the region of interest. Now with enzyme Cvn I, we can carry out diagnosis for sickle cell anemia. After cutting this particular amplified product with Cvn I, we run a small mini-gel and stain the gel. The beta-S fragment does not get cut, while two bands generated by a single cut of this fragment are the signature of the beta-A gene. There are also constant bands which are derived from other Cvn I sites in the region which are normally present. This is a relatively easy method that allows for diagnosis within several days after fetal sampling, if one is running this technique every day or two. Sickle cell anemia is a very simple genetic disease from the point of view of the geneticist as there is only one mutation that causes the disorder.

BETA-THALASSEMIA

To move to a more difficult diagnostic problem, let us discuss beta-thalassemia. A number of mutations are involved, and the disorder is prevalent in a number of ethnic groups. It is actually easier to remember the peoples *not* at risk for beta-thalassemia trait and beta-thalassemia disease, ie, Northern Europeans, Japanese and Koreans. Beta-thalassemia trait is found in about 3% of the world's population, or approximately 150,000,000 people. The disease is seen among Mediterraneans, American blacks, Middle Easterners, Indians, southeast Asians, South Chinese, and Indonesians. Instead of there being one point mutation causing the disease, as there is in sickle cell anemia, there are approximately 90 point mutations. We have considerable knowledge of these mutations and they are ethnic group specific. Of the 90 alleles, 30 are seen in Mediterraneans, 16 in Chinese, 10 in Indians, 12 in blacks, etc, and there is not much overlap of mutations among the groups. Also, we are

fortunate that there are a handful of mutations in each group that are common. Only six Mediterranean mutations account for 93% of the total of the beta-thalassemia genes in this group. In Chinese and southeast Asians, four account for 91%, five in Indians account for 90%, etc.

How do we detect these mutations? We now detect them directly and one approach is to make oligonucleotide probes, which are synthesized in the lab. These probes are short in length, usually around 20 nucleotides, preventing their hybridization to sequences differing by a single nucleotide. Thus, they can be designed to detect specific single nucleotide changes. We used to use oligonucleotide probes to detect single nucleotide changes to genomic DNA. Now the process is easier because we can amplify particular small fragments of DNA by PCR and ask the probe to find its specific complementary sequence in that smaller amplified fragment.

We make a short nucleotide probe specific for the mutant normal sequence. Since the mutant probe has a single nucleotide substitution, compared to the normal probe, it hybridizes only with the mutant gene. Conversely, the normal probe does not hybridize with the mutant gene because of this nucleotide mismatch, and that is what is meant by an allele-specific hybridization. If the DNA is dotted on a membrane after gene amplification and hybridized with a mutant probe, we can, for example, see the beta-thalassemia codon 39 mutation in a heterozygous mother. The mother is positive using both the mutant probe and the normal probe, so the mother is heterozygous for this particular mutation. The father is also heterozygous for this mutation. A control normal individual dotted in the same way hybridizes only with the normal probe and not with the mutant probe. A previously affected child has hybridization with only the mutant probe, demonstrating homozygosity for the mutation.

For some of these alleles, the same procedure described for sickle cell anemia can be done. We digest amplified DNA with a particular enzyme that detects the mutant site. If we cannot readily identify the mutation, the PCR product can actually be sequenced. Direct detection for beta-thalassemia is done routinely these days at our laboratory under Corinne Boehm's direction. Many families are having prenatal diagnosis in a number of pregnancies for this particular condition. One Greek couple we follow terminated affected pregnancies in 1982 and 1983, had a normal child in 1984, and then terminated two more affected pregnancies in 1986. After this series, the father called me to ask whether their risk was still one in four. We said, "yes, it actually still is one in four," and they did have another pregnancy with a good result.

In the last year it is very interesting to note that 80% of couples having prenatal diagnosis for beta-thalassemia have not had a previously affected child but were identified through carrier screening. Finding these couples is the goal if one is trying to prevent this particular disease. Prevention has

worked extremely well in the Mediterranean basin, where in many countries the frequency of the disorder has dropped 90% among live births compared to the rate ten years ago. In this country, the number of live births with this disorder is under 50% of the total recorded ten years ago. At the thalassemia clinic at Cornell University in New York, the staff used to see 10 to 12 new patients per year, and for the past two or three years they have been seeing about 1–2 new patients per year.

CYSTIC FIBROSIS

Direct detection of the mutations in cystic fibrosis (CF) soon will be possible also. At his A.S.H.G. lecture, L.C. Tsui will describe how the CF gene was isolated. At the moment Tsui, Collins, Riardon and their respective groups know of just one mutation that produces cystic fibrosis. There are going to be other alleles identified, but that particular mutation is a very common one in caucasians accounting for 70% of CF genes. (*Editor's note:* In July 1990, some 50 CF mutations are known, 49 of which have frequencies of <2% of total CF genes.) As with beta-thalassemia, an oligonucleotide specifically made to detect the mutation often detects homozygosity for CF in caucasians who have CF. This particular oligonucleotide detects many affected caucasians as positive. Using a normal oligonucleotide, the same individuals do not light up at all in this region, meaning that those individuals are homozygous for the mutation. Those who light up with both the normal and a mutant oligonucleotide are heterozygotes for this particular mutation and since they have CF they contain another, as yet unknown, CF mutation.

There is a big difference among blacks, as fewer will be positive with this particular mutant oligonucleotide and nearly all are positive using the normal oligonucleotide. About $\frac{1}{3}$ of black CF genes contain this particular caucasian mutation. We think there are other mutations in the black population and that this number can be explained somewhat by racial mixture. In our experience in Baltimore, about 80% of caucasians have this common mutation. The Baylor group estimates 75%. Having 75% of the CF mutations in caucasians of one type is useful, and means that about half the cases for prenatal diagnosis can be done by direct detection of this particular mutation. The other half will still be done by linkage analysis. In the next six months or so one would guess a large number of other common alleles ought to be identified.

DUCHENNE MUSCULAR DYSTROPHY

The story of gene diagnosis for Duchenne muscular dystrophy (DMD) began with the gene's isolation by Kunkel and Worton and their groups and the subsequent characterization of the protein, dystrophin. About 70% of defects are gene deletions, and those can be directly detected. Nearly all of

these can be detected swiftly by PCR techniques; the remainder can be detected by the Southern blot process. The remaining 30% of mutations are not deletions, and in those cases one has to do linkage analysis, which is informative and accurate. Carriers of deletions can usually be detected even when no affected male is available. Jeff Chamberlain et al at Baylor have looked simultaneously at nine different exons of the dystrophin gene using PCR to make sure those particular exons are intact. An individual can have a deletion of one particular band or be deleted for multiple bands. Because PCR analysis can be done, results can be available in a short period of time. Recently Kunkel, Beggs, and colleagues have expanded this analysis from 9 to 18 regions.

INDIRECT DETECTION

Linkage analysis is still being done in some disorders. Some studies for Duchenne muscular dystrophy and cystic fibrosis are done this way. This process requires preliminary family studies, although not necessarily an affected individual. The accuracy of diagnosis is good, but probably under 100%, and there are additional sources of error. Obviously paternity is important, and we also have to be concerned about recombination between our markers or polymorphisms and the particular mutation that is causing the disease. In other words, in this kind of analysis one is looking at markers, and not at the mutation that is causing the disorder. But this kind of analysis is generally applicable and accurate.

HEMOPHILIA A

With linkage analysis, it is key that the marker be very close to the gene of interest. If the marker is in the gene of interest or close to it, we are going to have a very small error rate due to recombination. If the marker is far away from the gene of interest, the error increases. For example, in the case of hemophilia A, if we use outside markers the recombination rate is on the order of 4% or so; with intragenic markers the error rate is essentially 0. If an obligate carrier for hemophilia A is concerned about the carrier status of her twin daughters, linkage analysis can be used. In such a family, an informative intragenic marker is found where the woman is $- +$, her affected son is $-$. Her identical twin daughters got the $+$ from her, so obviously they are not carriers. In this way we determine carrier status, and because the marker is within the gene of interest, the error rate is probably under 1%.

HUNTINGTON DISEASE

Let us turn our attention to the presymptomatic and prenatal diagnosis of Huntington disease (HD). The program for predictive testing at Johns

Hopkins in the Psychiatry Department has contacted approximately 350 individuals at risk for HD. Only 135 responded and set up an appointment. So, about $\frac{1}{3}$ of individuals at risk were interested in this kind of presymptomatic testing. Of those, 127 entered the study and had at least one appointment. The study protocol requires a number of appointments for psychiatric and psychological testing prior to the DNA testing. Genetic testing was requested by 110 persons, but some of these were clinically affected. They were excluded based on a good neurologic examination. That left 101 unaffected individuals, of which 31 still have not been analyzed. Seventy had an exhaustive DNA analysis with up to 12 markers studied, and 11 of those still remained uninformative. For these individuals, the family structure was not quite right for doing the analysis or there were not enough affected individuals, or the unaffected individuals were not old enough to be sure they were escapees from the disease. One can have Huntington disease with an onset of symptoms as late as 65–70 years of age. Now, of the 59 informative individuals, 43 tested negative, and 16 were positive. So, it has been interesting that it was not a one-to-one separation, and you might guess that we were lucky. We were probably dealing with many people who thought they were not affected and who were also somewhat older. In any case, the skewed results are hard for us to explain. Those individuals who were told that they likely have the disease seem to be coping well so far, according to the psychiatrists involved. I have not seen them personally, but there have been no untoward reactions that I know of to date in those 16 that tested positive.

Virginia Corson is going to talk later about prenatal diagnosis for Huntington disease, but I would like to discuss our experience with this disorder. In some families we are not able to do a presymptomatic test because only one affected individual is alive, however, exclusion testing is feasible. For example, if we identify the HD marker contribution to the son of an affected father and normal mother, we can see whether his offspring inherits the grandpaternal or grandmaternal pattern. If the affected grandparent's marker is transmitted to the fetus, the fetal risk for HD increases to approximately 50%. If the marker in the fetus comes from the unaffected grandparent, then the risk for HD is very low. So, in this situation we are not providing an absolute risk; we are not telling the couple that the fetus is affected if the grandpaternal marker is found. We are though increasing the risk to 50% and in half of their pregnancies we are essentially eliminating the HD risk. Again, this testing is all being done by linkage analysis.

SUMMARY

In 1989 we are continuing to move gene diagnosis over to the direct detection mode. We have sickle cell anemia, alpha-thalassemia, beta-thalassemia, Duchenne muscular dystrophy, Becker muscular dystrophy and

cystic fibrosis moved to direct detection with hemophilia B and alpha-1-antitrypsin deficiency soon to be there.

For indirect detection, we still have hemophilia A, and a comment on the genetics of hemophilia A is important. Remember that sickle cell anemia is caused by one mutation, while beta-thalassemia and cystic fibrosis have a finite number of alleles. Duchenne muscular dystrophy results from a different mutation for every affected individual, but most of these are deletions and can be directly detected. Hemophilia A is another X-linked disorder with almost every affected individual having a different mutation. That means that there probably are 100 ways to get beta-thalassemia and about 10,000 ways to get hemophilia A, so we need some really good novel techniques to detect these directly, and we are working hard on such techniques. I would not be surprised if hemophilia A moved into the direct detection category in the next year or so. We need to find the Huntington disease gene, and then it will move into the direct detection column. Neurofibromatosis is still in the indirect detection group but also may move very soon. Polycystic kidney disease is also still in the indirect detection column. This summarizes where prenatal and presymptomatic gene diagnosis stands in late 1989.

Issues Raised in Gene Linkage Studies

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INTRODUCTION

Coordinating linkage research studies is a relatively new role for genetic counselors. As human genome mapping projects exponentially increase, so will the demand for study coordinators with special genetic counseling skills. These linkage studies often involve single gene disorders, or categories of disorders, eg, collagen disorders like the osteogenesis imperfectas, familial cancers, Alzheimer disease, myotonic dystrophy; familial psychiatric disorders, such as schizophrenia and manic-depressive disorders; neurologic disorders, such as Huntington disease, Tourette syndrome, amyotrophic lateral sclerosis, idiopathic torsion dystonia, Parkinson disease; and other movement disorders (essential tremor, myoclonus). These categories of disorders may already be familiar to many genetic counselors working in specialty clinics. Now they provide an extended area for specialization and expansion.

Genetic counselors bring many special skills to the linkage study team. They are familiar with the genetics of these disorders, as well as the psychodynamic ramifications of each specific disorder. They are also trained to convey this often complicated body of knowledge to individuals and families with expertise that incorporates educational and counseling theories regarding the best way to deliver complex and emotionally charged information to people often facing crisis situations.

Of the 100,000 genes in the human genome, almost 1700 genes have been assigned to specific chromosomes [1]. Mapping of genes to a specific chromosome is done by various molecular genetic techniques: 1) family linkage studies, 2) chromosome studies, and 3) somatic cell hybridization studies [2].

For many hereditary diseases, the basic biochemical defect is unknown and therefore, the nature of the gene is unknown. In such instances, mapping the disease gene requires family linkage studies using DNA and other markers. The Huntington disease (HD) gene, assigned to chromosome 4 in 1983 [3], was the first in an exciting succession of disease genes that have been mapped via these family linkage methods. The abnormal gene product in HD has not yet been identified.

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WHAT IS A LINKAGE RESEARCH STUDY AND HOW DOES IT WORK?

Why study whole families with linkage methods? Why not just study 200 affected individuals diagnosed with the same disease?

1. Multifactorial Causes of Phenotype

Frequently patients report a mentally retarded relative who is 'mongoloid.' Investigations often reveal that the relative was mentally retarded and had various physical findings associated with mental retardation, but a chromosome test revealed a normal karyotype indicating that the relative did not have Down syndrome. Few diseases have a definitive test such as a karyotype. More often than not the diagnosis is clinical, based on symptoms. Much of clinical genetics is splitting phenotypes into different syndromes, or lumping variable expressions into the same syndrome.

2. Heterogeneity of Genetic Diseases

The same end disease condition can be caused by various abnormal genes in the pathway. The recent assignment of bipolar disease to a locus on the X chromosome in one family study [4] and to chromosome 11 in a family study of the Old-order Amish [5, 6] is an example. Using large families of affected individuals maximizes the likelihood that the same gene is being studied. The potential occurrence in a family of phenocopies does need to be considered, especially with disorders like dystonia and Parkinson disease, which can also be environmentally induced. In some particular cases within a family, the final diagnostic status of an individual in the linkage analysis may have to be coded as unknown, so as not to introduce error.

Mapping information has been particularly useful in the case of disorders for which the basic biochemical defect is not known, such as HD, cystic fibrosis, Duchenne muscular dystrophy, etc. Once a marker that is closely linked to the locus of a mutant gene is known, however, genetic diagnosis can be done by linkage analysis, which involves prenatal and preclinical sampling and carrier detection within a given family.

Later, with neighboring markers, one can 'walk in' on the segment of DNA that contains the mutant gene and thereby identify both the gene and the precise nature of the change, the so-called 'reverse genetics' approach. Knowing the nature of the mutated gene opens up the possibility of reconstructing the pathogenetic steps between gene and phenotype, and devising therapeutic measures for ameliorating the effects of the disorder.

PHASES OF LINKAGE STUDIES

Phase 1 linkage studies are directed toward searching the genome for a linked marker to the disorder in the families available for study, such as the

marker recently described for idiopathic torsion dystonia [7]. This phase of the search involves the use of highly polymorphic probes, linked sets of probes, and candidate genes. No results are available from phase I linkage studies. This can be exceedingly difficult to communicate to family members. It is important to have an explicit statement to this effect in the study consent form.

The work of the genetic counselor occurs mainly in phase 1, but there will be no phase 2, 3, or 4 unless phase 1 has been successful.

Phase 2 involves testing for the same linkage in other families [8], once a linked marker has been identified. This is an important phase of linkage studies and often requires hundreds of additional families before heterogeneity can be ruled out. This phase often engenders much frustration for family members who are aware of the exciting breakthrough of having identified a marker, yet face the agonizing wait of not being able to use this in a meaningful way for testing. Since there is no accurate way to predict how long it will take to proceed from phase 1 to phase 2 to phase 3, families are left with difficult decisions to make about childbearing and whether to delay starting a family until an accurate test becomes available.

In *phase 3*, which often begins simultaneously with phase 2, additional linked probes are sought to further define the genomic region containing the gene. This involves generating more probes from chromosome-sorted, genomic libraries, chromosome jumping and pulse field gel electrophoresis (PFGE).

If the gene location can be defined to a 2-10 cM region, *phase 4* studies can be undertaken to define genes within that region, isolate cDNAs for them and evaluate their possible role in the disorder. This work involves subcloning and restriction mapping of large genomic fragments, screening cDNA libraries, Northern blot analysis of the tissue distribution of corresponding mRNAs, and Southern blot and denaturing gel electrophoretic analysis of control and affected DNA.

Because the work of the genetic counselor is primarily in phase 1, this workshop will focus on details of phase 1 of a linkage research study.

ASCERTAINING AND CONTACTING FAMILIES

Families are ascertained by self-referral, after they have read an article on the study in a voluntary disease foundation newsletter, or by referral from specialized medical facilities or health care workers. Self-referral indicates motivation on the part of the patient or the concerned family member who contacts the study group. Referral by a doctor may not be as helpful, since the family may not be interested. However, with doctor referral, the diagnosis of the proband may be assured, and frequently the cooperation of the proband follows the referral.

In diseases such as amyotrophic lateral sclerosis (ALS or Lou Gehrig's

disease) and Parkinson disease (PD), 95% of cases are sporadic and only 5% of patients have family histories showing a familial form of the disease [2]. Articles about the study in disease-specific foundation newsletters or the lay press always elicit worried inquiries from patients who belong to the 95% of sporadic (presumed non-familial) cases, and they must also be offered genetic counseling. Some of this counseling can be done over the phone, but it requires the expertise of a genetic counselor to be delivered sensitively and accurately. Referrals to local genetics centers should be made when appropriate, documented with letters to the individual and/or referring physician.

Biostatistical analysis may be required to help determine which families will be the most informative and which should be studied first [9]. Families with large sibships and a greater number of meioses are sought (not easy in a country where women give birth to an average of only 1.9 children). Ideal populations do exist for linkage studies, including the Mormon, Amish, Mennonite and Venezuelan kindreds. More often than not, however, the populations or families available are less than ideal. The genotypes of missing sibs or deceased affected individuals can sometimes be 'reconstructed' by getting DNA from their spouses and children. This necessitates collecting four or five blood samples and explanations of why the blood of the spouse, who has no genetic relationship to the deceased affected sib, is required. Unaffecteds are told that it is just as important to study them as it is to study those who are affected.

It is helpful to identify key family members who can act as study advocates translating the study and the importance of participation to relatives. A variety of methods can be tried to inform all family members about a study, including phone calls, letters, family reunions and even videotaped messages by family leaders encouraging participation.

The decision by the investigators to include a family in the study should be made as quickly as possible. Families lose interest if there are delays between first contact and data and blood collection.

DATA AND BLOOD COLLECTION

The genetic counselor is primarily occupied with data and blood collection in a family linkage study.

1. The pedigree must be extensive, inclusive and accurate. It must include health information on every person as well as birthdate, deathdate if applicable, age of onset if affected, full name, address and telephone number. Some families have a family genealogist who can be helpful in constructing the pedigree. More than one informant may be needed in large families, one in each branch of the family. In X-linked recessive diseases, every sibship of affected males will have a different last name. Cooperation of the family leaders is important in large families and is essential when dealing with

families of certain ethnic backgrounds, eg, Asian families. Even with all the above information, contacting the family members will take time.

Everything genetic counselors have studied about denial, resistance and family members not speaking to each other applies to participants in family linkage studies and is magnified by the distance of relationship between the branches. Sometimes the family is emotionally close and in the same geographic area, and may even arrange a family reunion so the investigator can fly in to examine and draw blood from dozens of members all in one day. More commonly, the family is dispersed throughout the country.

Pedigrees of more than five generations cease to be the medical pedigrees most counselors are used to constructing in which the informant and living relatives knew all the members and the details. The pedigree becomes a genealogic pedigree filled with members that no living informant knew personally. To extend the pedigree into branches whose members have lost track and memory of each other, additional information is needed. Besides the information normally taken, the pedigree data collected should include everybody's full name, women's maiden names, birthplaces, residence(s), death places, approximate dates of birth and death, religions and occupations. These categories of data will be needed for genealogic research. A few large studies have even employed professional genealogists to help link distant branches of families. While the passage of generations does increase the chance of cross-overs and gene rearrangements, the knowledge that all the affected people in the extended pedigree are carrying the same mutation by descent permits the linkage study. This is especially true in conditions where death quickly follows onset and researchers have limited time in which to collect blood from affected individuals.

2. The diagnosis must be confirmed by medical records from qualified physicians or specialists. The counselor spends much time obtaining permission and sending for records. Autopsy records are valuable. In some studies, the research team will fly out to examine family members and draw blood. Videotaping may be necessary to confirm the diagnosis of an affected individual. In some disorders, the diagnosis may be 'certain,' 'probable,' or 'possible.' Follow-up visits may be needed. The investigators will start with a conservative definition of the disease and establish boundaries of the phenotype later. In the absence of biochemical markers for the disorder, control data may need to be collected to help define the disease phenotype.

3. Studies with blood collection at examination will generally require a larger budget than studies in which all blood is collected and sent by mail. The design of the study will depend on the likelihood of reliable diagnoses. Some studies are amenable to direct mail collection of samples whereas a difficult to diagnose disorder like dystonia relies on the expertise of a limited number of highly specialized neurologists.

Blood collection by mail can be satisfactory. The tubes should be sent out in

the packaging in which the blood is to be returned and accompanied by a letter of instruction, an informed consent form and a written explanation of the study. Tubes can be kept at room temperature until it is convenient for the person to have his blood drawn. Most affected people are seeing their physician at least a few times a year and having the blood drawn may be no problem. Unaffecteds often see a physician annually or even less frequently and may not be in a position to have their blood drawn without additional cost to them. If the study covers the cost of commercial laboratory phlebotomy, a major concern will be arranging a smooth method of payment between institutions.

4. Data collection, organization, and management in a family linkage study are extensive. Computerization is highly recommended.

DISEASE-SPECIFIC CHARACTERISTICS

Each disease has its own profile and specific characteristics that affect all aspects of the study and its design. Some of these characteristics include the age at onset, the duration and severity of the disorder and how the disorder impacts on family dynamics.

Onset. The age of onset may occur in childhood, as in dystonia; young adulthood, as in ALS or HD; or senior adult, as in PD or Alzheimer disease. The diagnosis may not be made until quite some time after the actual disease onset. Therefore, age at onset may affect the pedigree structure and number of relatives available for study.

Duration. The duration of the disease may be for the total of a normal lifespan, for the average 2–3 years elapsing before death with ALS, or for 10–15 years preceding death as in HD, PD, or Alzheimer disease. This will have a direct effect on the timing of exams and blood sample collection.

Severity. Severity of the symptoms may affect the quality of life. In dystonia, mild expression may be confused with normal movement. Other neurologic conditions may require the use of a wheelchair, or the patients may become so handicapped that they are housebound or must go to a nursing facility. If the disease leads to legal incompetency, consent must be obtained from next-of-kin.

Family dynamics. The psychologic dynamics of dealing with families with affected children is quite different from dealing with seniors who have developed Parkinsonism near the end of a full life. In psychiatric diseases and diseases with psychiatric symptoms in the advanced stages, the disease itself makes study more difficult. Family members are often ambivalent about participating. Informed consent by affected individuals may become more difficult to obtain.

COUNSELING CONSIDERATIONS

The counselor who is contacting the families to enlist participation must recognize that anxiety accompanies linkage studies. That the disease study exists reinforces the fact that the disease is genetic and that it has direct ramifications for an individual or family. This raises the anxiety of family members regarding genetic risks to themselves, to their children and to their relatives. These same anxieties may become a large part of the impetus for cooperation in support groups, registries and research studies. In some instances they also need to be addressed as a genetic counseling issue with formal or informal genetic counseling.

Substantial effort is required of participants. They must arrange for the study coordinator to receive their medical records or they must be examined. They must arrange for their blood to be drawn. They answer questions and may have to think about things they would rather not think about.

Basic genetic principles, and sophisticated linkage analysis are a source of confusion to the families. Most people do not understand chromosomes, genes, or DNA.

Even though they don't understand how DNA may be related to the disease, most people cooperate in the study because it is seen as an effort to help themselves or their family. They are told that the study may be of no direct benefit to them in the management of their condition, but may be of benefit to their children and other family members, and certainly to future generations.

Communication of Progress to Family

We have found progress reports to be an exceptionally important and often overlooked component of these studies. There are no results about DNA status, but it is nonetheless important to report progress and to reinforce the importance of participating in such a study. This encourages extended familial involvement in the study and fosters a feeling of communication and collaboration between family members and researchers. Progress reports may include friendly progress letters to families, articles in disease-specific foundation newsletters, talks at support group meetings or direct mailings to all study participants. When the study is published, a direct mailing should be sent to all participants with an abstract or reprint of the paper.

These communications also erode misconceptions about the study or the disorder, which may act as barriers to family members cooperating. Some examples include a family member who is reluctant to participate because he thinks that if he gives blood he will be at risk for AIDS . . . or a family member who is afraid that if you examine him, his children will get the disorder . . . or a 'door-slammer' who knows deep down that he has the disorder, has several children, and who does not have the education or the family support systems to deal with the guilt involved in directly confronting the situation. This is

particularly common with a disorder like dystonia, where there may be highly variable expression within the family.

The participants must feel secure that all information given and discovered is confidential, even discoveries of gene carrier status (affectedness) or of nonpaternity. Special care must be taken to avoid unintentional disclosure of disease status between family members. Even when on a field trip, you have to be careful not to let others unintentionally view your itinerary, or overhear telephone conversations with their relatives to get directions. It is helpful to ask family members to share participation with other branches, but not all families will be comfortable doing this, and you should be extremely careful to respect their needs.

Some family members need to ventilate emotions. Allowing them an opportunity to do so is part of the counselor's job. Talking with more than one family member at a time can interfere with counseling. Counseling therefore requires much time and privacy. The counselor functions as the patient's advocate on the study team. The patient must be seen as a human being who happens to have a genetic disease and not solely as a research subject.

RECOMMENDATION

To help genetic counselors and others keep up with advances, it would be helpful to have a national computerized repository that lists all research linkage protocols and contact persons.

CONCLUSION

The main issues raised by linkage research studies are no different than the myriad difficult social, ethical, religious and interpersonal issues raised by the presence of genetic diseases in families and can be dealt with within the same ideologic frameworks on which the genetic counseling profession has developed. Sensitivity to the needs and goals of researchers and family members, as well as commitment to timely, honest and direct communication between all involved will yield study results of the highest quality.

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Prenatal Testing For Huntington Disease

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Restriction enzyme analysis has expanded the list of diseases amenable to prenatal diagnosis from common chromosome abnormalities, ie, Down syndrome, and metabolic disorders, ie, Tay-Sachs disease, to detection of problems with variable sequelae. Many genes have been located or localized to chromosome regions, and families at risk for disorders such as cystic fibrosis, Duchenne muscular dystrophy, hemophilia and sickle cell disease have new options for carrier or prenatal testing.

In the same manner, families with a history of Huntington disease (HD) have sought prenatal diagnosis. This debilitating, autosomal dominant neurologic disorder typically manifests between the ages of 30–50 years with progression of symptoms from choreiform movements, memory loss and mood swings to the eventual deterioration of the nervous system. Until recently, an individual at risk has usually made reproductive decisions before knowing whether the gene has been inherited. Many persons went ahead and had children in spite of the risk, while others decided *not* to have offspring knowing that there was a 50% chance that they had *not* inherited the gene.

In 1983, the gene for HD was localized to the short arm of chromosome 4 based on pedigree studies of a large family in Venezuela. This development opened up the possibility of testing asymptomatic adults who desired information about their status. Several centers, including the Johns Hopkins Huntington Disease Project, limited testing to individuals living within a certain geographic radius who could participate in a multi-visit protocol. In contrast, restriction enzyme analysis for prenatal testing was offered without this restriction.

In the families evaluated to date at Johns Hopkins for prenatal diagnosis, DNA studies have been sought by at-risk prospective parents to determine whether gene markers from the affected or the unaffected grandparent were transmitted to the fetus. Thus, the testing does not provide information about the at-risk adult's status, but will increase or decrease the 25% fetal risk for HD. For example, the pregnant woman in Figure 1 is at 50% risk for HD herself, while the fetus is at 25% risk. Presymptomatic testing using linkage analysis is not possible as she has only one affected living relative; however, DNA studies can differentiate the woman's paternally (B) and maternally-

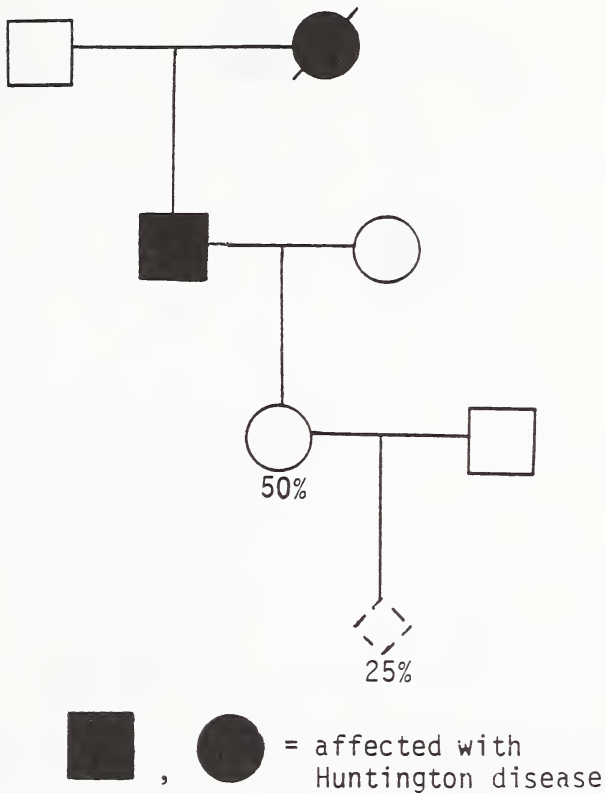


Fig. 1. The fetal risk for Huntington disease is 25%.

derived (D) chromosome #4 regions and then can be used to modify the fetal risk (Fig. 2). In this pedigree, the marker from the unaffected grandmother has been transmitted; thus the fetal risk drops from 25% to close to 0. If, on the other hand, the analysis showed that the chromosome 4 marker from the affected grandfather was transmitted (B), the risk for HD would increase from 25% to nearly 50%. Thus, even though the patient does not know whether she has inherited her father's HD gene, prenatal studies can exclude the diagnosis for the fetus or raise the risk to that of the pregnant woman's. The accuracy of these results is currently 95–99%, allowing for the possibility of recombination between the linked marker and the HD gene.

We have counseled four couples regarding the option of prenatal diagnosis for Huntington disease. Two of the women were pregnant at the time of their visit; the other two were interested in childbearing if DNA studies could be used to evaluate the fetal risk for HD. Three couples stated that they would

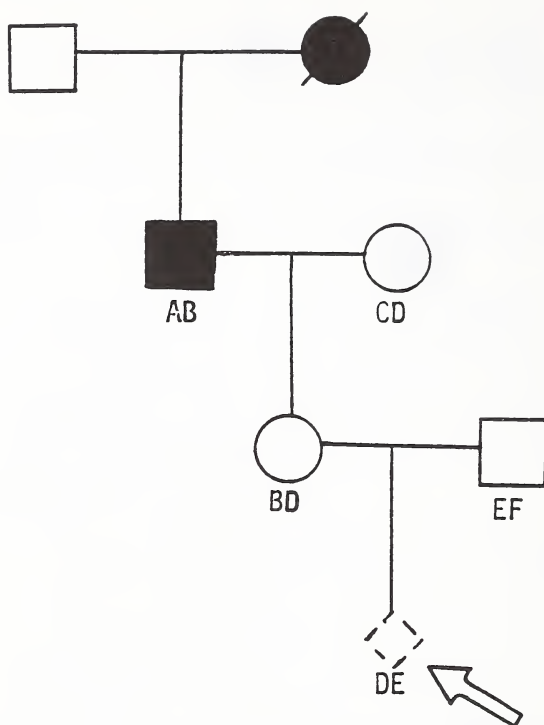


Fig. 2. The fetus has inherited marker D from the unaffected grandparent, dropping the risk for HD to near 0. If marker B had been present, the risk would be close to 50%.

seek elective termination if the fetal risk for HD were increased from 25% to 50% through prenatal testing. The other couple believed that they would not abort in such a circumstance.

When our center began to offer prenatal testing for HD, discussions with the psychologists and psychiatrist most directly involved with the presymptomatic testing project led to a consensus that the prenatal studies should be offered only to those couples who would consider termination if the results were indicative of an increased fetal risk. This philosophy is contrary to most genetic counselors' "non-directive" approaches, but was based on several considerations unique to HD.

First, presymptomatic testing for HD is *not* being offered at Johns Hopkins to children under the age of 18. It is felt that each individual at risk should be allowed to make a personal decision about when, and whether, to pursue such testing and that the decision should not be made by one's parents. In fact, for a variety of reasons, far fewer at-risk adults have chosen to be tested than was

predicted before DNA studies were available. With regard to prenatal diagnosis, if a couple has testing and continues the pregnancy when the fetal risk is increased to 50%, the information will result in a presymptomatic diagnosis in the child if the at-risk parent subsequently develops symptoms.

Another concern revolves around the possible pathologic sequelae for the family if the at-risk parent develops symptoms of HD and must then deal with the guilt of genetic transmission, in addition to a personal psychiatric instability. Our specialists believe that the parent-child relationship could be adversely influenced by the knowledge that a child has inherited the HD gene.

One couple in our sample sought counseling early in a semi-planned pregnancy two years after the patient's father was diagnosed with HD. They chose to proceed with family studies and an informative marker was found before her scheduled chorionic villus sampling. An exclusion of HD for the fetus was made by linkage analysis and the couple continued the pregnancy.

Two patients sought genetic counseling and DNA family studies prior to pregnancy. Neither couple wished to have children at risk for HD and would therefore *only* attempt childbearing if prenatal diagnosis were available. In fact, one of these women waited two years before becoming pregnant until an informative marker for her family could be detected. Her first pregnancy resulted in elective termination after DNA studies raised the fetal risk to 50%. In the couple's subsequent pregnancy, an exclusion of HD was made, and they recently gave birth, reassured that their daughter's risk for HD is less than 1%. The other patient has had one pregnancy to date with HD excluded by DNA studies of villus tissue.

The couple that would not terminate in light of an increased risk was counseled about nondisclosing prenatal diagnosis. Although they were hoping for reassurance through an exclusion diagnosis, they agreed that if the fetal risk were raised to 50% and they continued the pregnancy, this information would place added stress on their family. Testing was declined.

Overall, our laboratory has received a total of nine samples for nondisclosing prenatal diagnosis of HD. In five pregnancies, the fetal risk was reduced to less than 5%, and the pregnancies were continued. In the remaining four pregnancies, the fetal risk was increased to approximately 50% and three couples chose therapeutic abortion. One couple elected to continue the pregnancy after a period of difficult decision making. They will thus live with the knowledge that if the diagnosis of Huntington disease becomes evident in the at-risk husband, the child will ultimately face a similar fate.

The issues raised by the availability of prenatal testing for autosomal dominant disorders such as neurofibromatosis, Marfan syndrome, polycystic kidney disease and Huntington disease will be, in some ways, different and perhaps more complex than those traditionally faced by genetic counselors and our patient families. The concepts of risk and burden still apply, but

quality of life considerations seem more difficult to address. For most of these dominant disorders, diagnosis in childhood is usually available and medically advisable. For HD, we believe that no real benefit is gained by diagnosis prior to adulthood or, at least, the age of reproductive activity. If no advantage is apparent through early testing, should prenatal testing be offered to couples who would not abort if an exclusion is not made?

We feel that the issue of pregnancy termination should be specifically addressed in the genetic counseling session with at-risk individuals seeking prenatal diagnosis for HD. Families clearly expressing a desire to continue pregnancy regardless of prenatal test results should be encouraged to forego these studies for the reasons discussed. For these families, the wish to be reassured through prenatal testing is not worth the burden of hearing bad news that does not affect the outcome of pregnancy.

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Genetic Counseling Issues In The Use Of DNA Analysis For Duchenne/Becker Muscular Dystrophy

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INTRODUCTION

Genetic counseling issues arising from molecular genetic analysis of nine families with Duchenne/Becker muscular dystrophy (DMD/BMD), as well as general implications for genetic counseling in DNA testing, are presented here. DMD is an X-linked recessive disease that usually affects males and is lethal in early adulthood.

DMD/BMD is characterized by the inability to produce a 427 Kd protein, dystrophin [1]. Dystrophin is encoded by the largest known gene of approximately 2 million base pairs [2–6]. One third of all DMD cases represent new mutations in the dystrophin gene [7]. With the cloning of the DMD gene [2, 8, 9], molecular probes became available for linkage analysis using restriction fragment length polymorphisms (RFLPs) [10–12]. In addition, cDNA probes [5] to the entire DMD gene could be used in screening males to detect deletions and duplications that account for 50% to 70% of the mutations that occur in this large gene [5, 13–17]. Long-range physical mapping of the gene has enabled carrier detection in females using pulsed field gel electrophoresis (PFGE) [3, 6, 18–20]. More recently, multiplex DNA amplification of selected exons has been used to detect deletions in males [21]. Results of DNA analysis are used in combination with creatine phosphokinase (CPK) levels and pedigree information to provide a probability of carrier status or prenatal diagnosis to interested families.

METHODS

Counseling Methods

Nine of 11 families were tested; none of them had previous genetic counseling or DNA testing. Initial contact with each family began with a telephone call to the mother of an affected child. The study was described as a DNA test for DMD/BMD, which would analyze carrier status. At the initial meeting, a family pedigree was obtained and an agreement was made that

families would attend the initial genetic counseling session lasting about 90 minutes, including the specimen collection and another open-ended session, which would involve communication of results. Further access to the counselor was assured via a toll-free telephone line. A letter explaining the agreement was provided to all participants and a consent form explained and signed by all participants prior to the initial genetic counseling session.

During the first genetic counseling session, the family's previous knowledge of DMD, its inheritance pattern and previous carrier detection methods were assessed. Then, a careful review of the X-linked recessive pattern of inheritance was given including a basic explanation of genes, chromosomes and heredity. Because of their interest in dystrophin, there was discussion of the dystrophin gene and its role in the disease pathology. DNA testing was briefly explained. The major discussion of DNA testing was reserved for the second session. The goal of carrier analysis, especially for mothers of sporadic cases and sisters of boys affected with familial DMD was discussed. CPK was measured in all females. Most of the families had already experienced CPK testing for carrier detection through the neurologic clinic, and those with normal values were aware that their carrier status was still in question. The importance of paternity was explained in the group setting. An opportunity to decline testing was given privately to females who participated. The laboratory also has the capability to test for nonpaternity or to distinguish monozygotic from dizygotic twins by variable number of tandem repeats (VNTR) probes if needed.

Following the first genetic counseling session, medical records including muscle biopsy report, EMG and CPK values were reviewed. The natural history of the disease distinguishes DMD from BMD (wheelchair confinement before 12 years of age in DMD) as DNA testing does not. A second genetic counseling session was held with each family and test results were reviewed. DNA testing was explained in more detail. Carrier status, prenatal testing, further testing options and reproductive alternatives were important areas of interest for the families.

DNA Analysis Methods

Methods of DNA analysis are detailed in Richards et al [22]. Each case was unique and required an individualized strategy for analysis. The strategy was designed to combine deletion analysis with linkage analysis. When a deletion was found initially by the polymerase chain reaction (PCR) technique, it was confirmed by cDNA analysis. When there was a large deletion, pulsed field gel electrophoresis (PFGE) was carried out on females for carrier status. When a small deletion was found, scanning densitometry was used to detect carriers. In the report format, the X chromosome was represented graphically as patterned bars. Sixteen polymorphisms both inside and flanking the DMD

gene were used to follow the X chromosomes through a family in linkage analysis. Risk assessment was done using the computer program LINKAGE.

RESULTS

The pedigree of each family and their DNA results are shown graphically in Figure 1. In *Family 1*, a familial case of DMD, no deletion was found. The daughter was found to be a carrier by linkage analysis because she inherited the same X chromosome as the affected boy. The mother's twin half-sisters were shown to be identical twins using DNA fingerprinting by VNTR probes with greater than 99.6% probability. The full sister inherited a different X chromosome and, therefore, was not a carrier. The mother of the affected boy

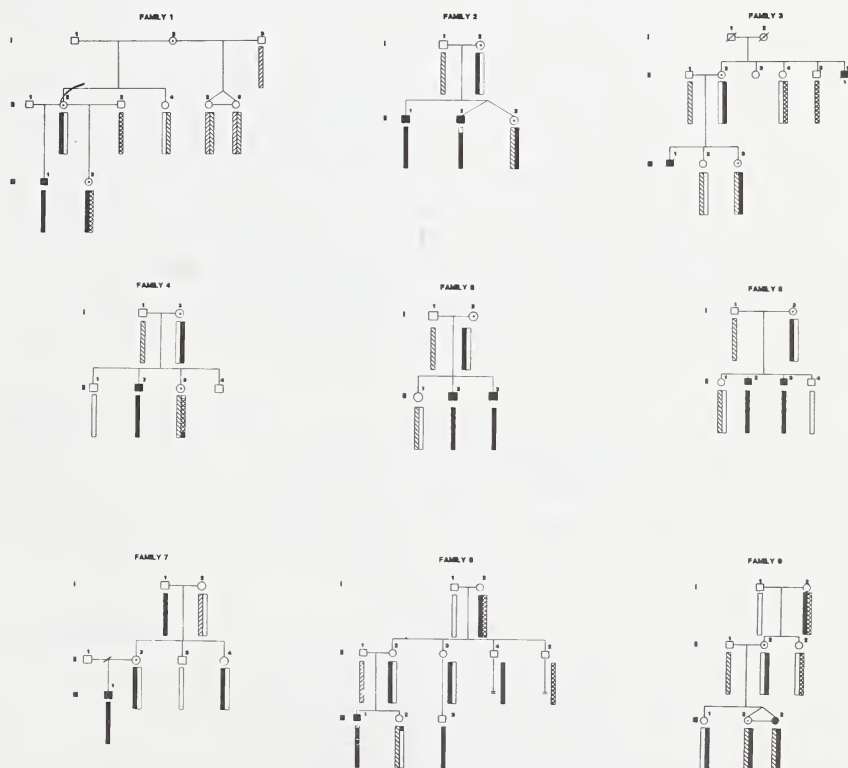


Fig. 1. Linkage analysis. The key reflects the 16 polymorphisms which may be used in this analysis. The bars represent chromosomes. The probes that are intragenic include (from top to bottom) J-66 through pERT87-1. The extragenic probes are C7 and 99.6 telomeric, and 754 centromeric.

does not use birth control and felt she would not undertake prenatal diagnosis as she would not terminate an affected pregnancy. She was encouraged to seek prenatal care prior to undertaking a pregnancy.

Family 2, also with familial DMD, was found to have a deletion. There was a cross-over in the male twin. Both mother and daughter, with elevated CPK, were found to be carriers.

There was no living affected member in *Family 3*. The mother was an obligate carrier who had five deceased affected brothers. The need to request participation of other family members while testing was underway led to a policy to request all who would be necessary for a diagnosis prior to initiating testing. One daughter was found likely to be a carrier by linkage analysis.

Family 4, also a familial case, had a deletion detected in the affected boy. By scanning densitometry, both mother and daughter were found to have the same deletion and therefore are carriers. An extensive discussion of abortion ensued because of the carrier status of the daughter.

Family 5 was also a familial case. A deletion using both cDNA and genomic p20 probes was detected in both boys and their mother. Their sister did not have the deletion and, therefore, is not a carrier. The mother uses no method of birth control and would not have prenatal diagnosis, because she would not risk miscarriage of a pregnancy.

Initially, one boy was affected in *Family 6*, and the case was considered sporadic. Genomic probes pERT 87-1, 87-8, and 87-15, as well as cDNA probes 2-3 and 4-5a detected deletions in the affected boy, an undiagnosed younger brother and their mother proving the mother to be an obligate carrier. The sister of the affected brothers was found to be a non-carrier by densitometry scanning.

Family 7 was a sporadic case and no deletion was found. The affected boy inherited the grandpaternal X chromosome. The mother of the affected has had markedly elevated CPKs since age 15 and is likely a carrier. Her sister also inherited the grandpaternal X chromosome. Therefore, the possibility of gonadal mosaicism in the grandfather affects the sister, giving a risk of approximately 5–10% for carrier status [23].

In *Family 8*, a sporadic case, a deletion was found in cDNA in the affected boy only. Different cross-overs were found in the affected boy and his sister; a 2-year-old cousin, considered normal, and a normal maternal uncle were found to have the same X chromosome. The mother of the affected male also had a risk of carrier status due to germline mosaicism.

A severely affected female monozygotic twin in *Family 9* was found to have a deletion as did the twin sister and their mother. The maternal grandmother, aunt and another sister did not show the same deletion. Therefore, we proposed that the mutation began in the mother. The twins were found to be identical by DNA fingerprinting. There was no translocation or uniparental

disomy and an extended research study showed uneven Lyonization as the underlying mechanism causing the affected twin's disease.

DISCUSSION

A number of conclusions were drawn from the results of the testing. All normal males included in DNA analysis should have at least one normal CPK value and test request format should document the medical diagnosis carefully. DMD/BMD diagnosis documentation is essential because DNA testing does not distinguish DMD from BMD nor does it distinguish DMD/BMD from other muscular dystrophies. Results of DNA analysis should be given personally by an experienced professional with consideration of referral sources that may be needed for family support. Reliable preconceptual selection techniques will be important for carriers in the future.

Complex terminology such as germline mosaicism, cross-over and recombination, and uninformative probes must be clearly explained to the lay person. Graphic illustration is helpful and a graphic report format enables families to see how the DMD gene travels through a family. Variation in educational levels, socioeconomic levels, cultural and religious values all need to be considered by the genetic counselor. Financial concerns and questions regarding health insurance coverage for prenatal vs. carrier testing are still unresolved. Finally, as technology changes certain equivocal cases might benefit from further testing, particularly sporadic cases in which no deletion was found.

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The Usefulness of Cytogenetic and DNA Linkage Analysis in Counseling Families with Fragile X Syndrome

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INTRODUCTION

Fragile X is the most common inherited form of mental retardation with an estimated incidence of 1/1,000 in males (Herbst and Miller, 1980; Webb et al, 1986), and 1/750 in females (Opitz, 1986). As a newly recognized condition, many questions still remain regarding diagnosis and treatment. The work of Sherman et al (1984; 1985) has assisted genetic counselors in providing recurrence risks and yet important genetic concepts such as the mechanism of inheritance remain unclear. In spite of continued improvements in our understanding of fragile X syndrome and cytogenetic and DNA techniques, carrier testing remains imperfect and is further complicated by nonpenetrance and variable expressivity in both males and females. Although prenatal diagnosis is available, the reliability and accuracy depend on the procedure used, cytogenetic studies, DNA linkage analysis and clinical assessments of appropriate family members.

The Fragile X Project recently completed comprehensive testing on 22 fragile X families. Initially, families had undergone genetic counseling based on clinical evaluations and cytogenetic analysis. Because this information was critical for reproductive decisions, most families had requested cytogenetic or DNA testing prior to pursuing a pregnancy. More recently, families were offered DNA linkage analysis to complement previous studies and to provide individuals with more accurate prenatal testing when appropriate. Several cases are presented to demonstrate how DNA linkage analysis influenced genetic counseling. In addition to a review of fragile X inheritance and available testing, the importance of preconceptional counseling will be discussed.

REVIEW OF INHERITANCE

Large population studies have clearly documented a preponderance of males with fragile X syndrome. With no evidence of male-to-male transmis-

sion, fragile X syndrome was first considered an X-linked recessive trait (Sherman et al, 1984). More recently, others have suggested X-linked semi-dominant (Brown et al, 1987a) or perhaps X-linked dominant inheritance (Mulley and Sutherland, 1987) as equally likely possibilities. In any case, there are a number of characteristics of fragile X inheritance that are atypical when compared to any other known X-linked disorders.

It is well established that females can be affected, though usually to a lesser extent (Escalante and Frota-Pessoa, 1973; Hagerman et al, 1986; Turner et al, 1980; Webb et al, 1982). Investigations by Sherman et al (1984) have suggested that one third of all heterozygous fragile X females are mentally retarded. Perhaps as many as half of the remaining two thirds have more subtle learning disabilities (Kemper et al, 1986; Wolff et al, 1988). Sherman et al (1985) also have shown that a female's mental impairment in some way influences her risk to have affected offspring. For example, a mentally impaired mother has a 50% risk to have a son with mental retardation while a normally functioning mother has a 38% risk to have an affected son. Similarly, the risk of mental impairment in a daughter of a mentally impaired mother is 34% compared to 16% for a nonimpaired mother.

Families exist in which the gene has passed through normally functioning males or transmitting males. The concept of nonpenetrant or transmitting males has been suggested by several authors (Brondum-Nielsen et al, 1981; Camerino et al, 1983; Fryns and Van den Berghe, 1982; Jacobs et al, 1983; Martin and Bell, 1943). It is now established that 20% or more of all males who carry the gene are unaffected cognitively (Sherman et al, 1985; Sved and Laird, 1990). Mothers and daughters of nonpenetrant males are both intellectually normal yet the penetrance of mental impairment is higher in the offspring of these daughters than in the mothers of nonpenetrant males (Sherman et al, 1985). This unusual finding is known as "Sherman's Paradox" (Opitz, 1986). Although theories exist that may explain Sherman's Paradox and the other observations noted above (Friedman and Howard-Peebles, 1986; Israel, 1987; Laird, 1987; Nussbaum et al, 1986; Pembrey et al, 1985; Steinbach, 1986), the understanding of fragile X syndrome's inheritance is only one facet of the genetic counseling challenge.

CARRIER TESTING

Cytogenetic Testing

The definitive diagnostic test for fragile X syndrome is chromosome analysis. Lymphocytes cultured and prepared using previously described techniques (McGavaran and Maxwell, 1983) are known to elicit the fragile site in 99% of all affected fragile X males and approximately 90% of affected fragile X females (Sherman et al, 1984). Although previous reports have argued about

whether a correlation exists between the percentage of fragile X expression and IQ in males or females (Chudley et al, 1983; Cronister et al 1991a; Jacobs et al, 1980; Mattei et al, 1981; Turner and Partington, 1988), normal functioning fragile-X heterozygotes and hemizygotes are frequently fragile-X negative or low expressors (Laird et al, 1990; Sherman et al, 1985).

When chromosomes for fragile X were originally analyzed by looking at conventionally stained cells, expression of 4% or greater was considered a cut-off for diagnostic purposes (Howard-Peebles, 1981; Jacobs et al, 1980). As more laboratories chose G-banding techniques, 1–2% fragility was considered sufficient to positively identify a fragile X carrier (Fryns and Van den Berghe 1983; Herbst et al, 1981; Sherman et al, 1984; Vekemans et al, 1983). However, other investigators (Hogge et al, 1984; Marlhens et al, 1986; Popovich et al, 1982; Proops and Webb, 1981; Shapiro and Wilmot, 1985) have raised concern about occasional observations of fragile X expression in control bloods and amniocytes. Perhaps these reports represent expression of a common fragile site at or near Xq27 as suggested by Ledbetter and Ledbetter (1988). Sutherland and Baker (1990) have subsequently shown a fragile site at Xq27.2, which can occur in 1% to 4% of normal patients and which can be differentiated from the fragile site at Xq27.3 seen in patients having fragile X syndrome. Although most experienced laboratories now agree that 1% to 3% fragile X expression is diagnostic, if repeatable, caution must be exerted when counseling low expressing, but phenotypically normal individuals (De Arce et al, 1986; Jenkins et al, 1986; Ledbetter and Ledbetter, 1988; Soudek, 1986; Turner and Jacobs, 1983).

DNA Linkage Analysis

DNA linkage analysis has been helpful in carrier detection in the nonexpressing, normal functioning, fragile X carrier. Significant work over the past few years has contributed to the detection of probes proximal and distal to the fragile X locus (Brown et al, 1988; Dahl et al, 1989; Hofker et al, 1987; Oberle et al, 1987; Patterson et al, 1988; Thibodeau et al, 1988; Veenema et al, 1987; Winter and Pembrey, 1986). Difficulties in cloning near the region of the fragile X locus, however, have slowed progress in providing a more detailed genetic and physical map of this region. Nevertheless, it is generally agreed that the most probable order for some of the loci identified in this region is the following:

DXS51-F9-DXS105-DXS98-DXS369-FRAXA/
(52A) (55E) (4D-8) (RN1)

DXS296-DXS304-DXS305-DXS52-F8/DXS115
(VK21) (U6.2) (1A1) (ST14) (767)

The usefulness of the probes that identify these loci differs for each family and is dependent upon which restriction fragment length polymorphisms are

informative (ie, heterozygous in females). Additionally, differences in the recombination fraction among the fragile X population (Brown et al, 1987b) have made linkage analysis more difficult. Linkage heterogeneity has been shown for the DNA probes F9 and 52A, on the proximal side of the fragile X locus (Brown et al, 1987b). An insufficient amount of data is available, however, for the probes closest to the fragile X locus (4D8, RN1, VK21) to know whether there is any linkage heterogeneity in this region as well. It is clear that the true recombination frequency, including the degree to which double recombination occurs, and the degree of heterogeneity for many of these markers is still unknown. In general, given participation by multiple relatives, useful data can be obtained on most families being studied. Hopefully, as new and closer DNA probes become available, both the degree of informativeness and the accuracy of the linkage studies will improve.

When calculating specific carrier risks from DNA studies the computer program LINKAGE is commonly used. It is important to understand that the usefulness and accuracy of this program depend on the specific information entered (Lathrop and Lalouel, 1984). Important parameters entered are penetrance figures, which are typically based upon the work of Sherman et al (1984; 1985), mutation rate and recombination frequencies. Because of confusion as to the nature of the mutational event leading to fragile X syndrome, most laboratories use either zero or 2.4×10^{-4} per gamete per generation as the new mutation rate (Sherman et al, 1984; 1988). With the exception of isolated cases (apparent new mutations), the mutation rate will not significantly influence carrier risks. Finally, and perhaps most critical, is the entering of accurate information regarding cytogenetic testing, cognitive testing and physical examination on as many relatives as possible.

PRENATAL DIAGNOSIS

Prenatal diagnosis is now available to all fragile X families. Strict guidelines for culture techniques outlined by Jenkins et al (1988) and Purvis-Smith et al (1988) greatly increase the accuracy and reliability of this procedure.

Prenatal fragile X cytogenetic analysis is currently performed at only a few centers throughout the country. Since amniocentesis is widely available, our greatest prenatal diagnostic experience is in using this procedure (Jenkins et al, 1988; Purvis-Smith et al, 1988; Shapiro et al, 1988). Although experienced researchers are hesitant to quote reliability figures, prenatal cytogenetic analysis is considered 92%–95% accurate (Brown et al, 1987a; McKinley et al, 1988). The greatest concerns are both the false-negatives and false-positives (usually low expressors) previously reported in the literature (Jenkins et al, 1988; Purvis-Smith et al, 1988; Shapiro et al, 1988; Tommerup et al, 1986). To avoid these ambiguous results, DNA linkage studies, which can complement the cytogenetic studies, are recommended. DNA analysis performed in

combination with cytogenetic studies can raise the accuracy of the procedure to as high as 98%–99% (Brown et al, 1987a; Jenkins et al, 1988; Oberle et al, 1985; Shapiro et al, 1988).

An alternative procedure is chorionic villus sampling (CVS). Although there has been some debate over the risk of this procedure, Rhoads et al (1989) examined the safety of CVS in 2278 women and estimated the excess risk to be 0.8%. It is an appealing technique because it can be offered earlier in pregnancy. Again, both cytogenetic and DNA testing can be done using this tissue. However, if DNA testing is not possible, a negative or questionable result on cytogenetic analysis requires repeat confirmation in another tissue (Jenkins et al, 1988; Shapiro et al, 1988).

The third available procedure is percutaneous umbilical blood sampling (PUBS) or fetal blood sampling. This technique has generally been used to confirm results from CVS or amniocentesis. Theoretically, this is the most accurate means for cytogenetic detection of the fragile X chromosome. Availability, timing of the procedure (often after 20 weeks gestation) and our inability to perform DNA analysis on this tissue are viewed as serious drawbacks (Shapiro and Jenkins, 1988). Butler et al (1988), however, have successfully performed PUBS as early as 17 weeks gestation and both Webb et al (1987) and Butler et al (1988) have successfully performed PUBS and amniocentesis simultaneously. Nevertheless, more time and experience is necessary to clarify this procedure's usefulness and safety as a prenatal diagnostic technique.

CASE PRESENTATIONS

Example 1 (Fig. 1)

Case FX-30 is a good example of how DNA linkage analysis complements chromosome analysis for carrier detection. II-2 and II-3 presented as two intellectually normal sisters of a known fragile X male. Chromosome results on both individuals were 0/200 cells fragile X positive. II-1 is the only individual in the extended family who has been diagnosed with fragile X syndrome. When we first counseled this family in 1984, it was generally agreed that mothers of affected males were obligate carriers. Consequently, using Bayesian analysis, II-2 and II-3 were each given approximate recurrence risks of 40% $[(.5)(1-.32)/(.5 + .5)(1 - .32) = .4]$. If we incorporated the probability that these females were fragile X-negative, we could lower their individual risks to approximately 31%. This is based on work by Sherman et al (1984) which suggests that 26% of normal functioning females are fragile X-positive. We typically avoid adding in this probability since laboratories may vary in their distribution of fragile X-positive to fragile X- results among negative normal obligate heterozygotes. DNA linkage analysis was later

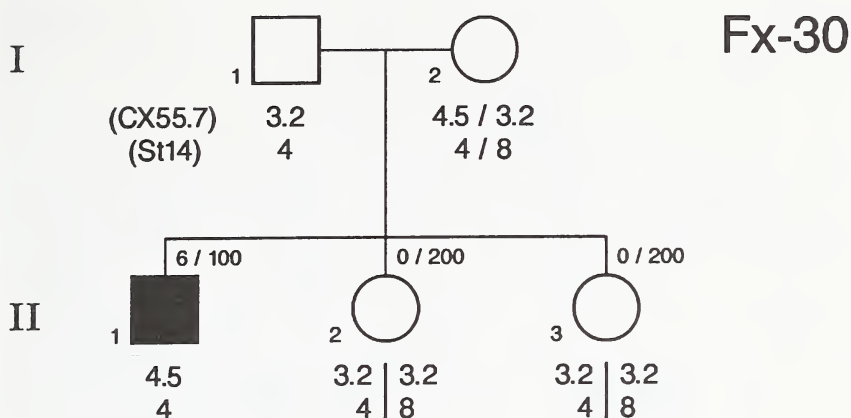


Fig. 1. Fragile X pedigree in which II-2 and II-3 are shown to be noncarriers by DNA linkage analysis. Solid indicates mental retardation.

completed for this family. Using the M link option of the computer program LINKAGE (Lathrop and Lalouel, 1984), the probability II-2 and II-3 are noncarriers is 0.99 (mutation rate entered as 2.4×10^{-4}).

Example 2 (Fig. 2)

Case FX-07 is another example of the usefulness of DNA linkage analysis. I-2, II-3, II-5, and II-7 all were found to be cytogenetically negative for the fragile X chromosome. II-1, also 0/200 fragile X-positive, had sought genetic counseling to find out her risk of being a carrier. From DNA family studies, I-2 was shown to have a 0.98 probability of being a nonpenetrant male (mutation rate equals 2.4×10^{-4}). Accordingly, II-1 was counseled as an obligate carrier. Importantly, DNA results on her will be available for prenatal diagnosis, an option this couple is seriously considering.

Example 3 (Fig. 3)

Case FX-39 first sought genetic counseling in early 1984. Chromosomal work-up of numerous relatives revealed I-2, II-2 and III-6 to be fragile X-positive in 1 of 200 cells counted. Based on an established family history of fragile X syndrome diagnosed in IV-2 and cytogenetic data on IV-1, these individuals and III-2 were counseled as being normal fragile X carriers. More recently, DNA linkage analysis was performed to confirm these results. Surprisingly, these studies strongly suggested (probability of 0.8816) that II-1 is a nonpenetrant male. Further work-up of his family with DNA markers closer to the fragile X locus is critical to confirm this suspicion. More importantly, DNA linkage analysis provided III-6, who was considering future pregnancies and prenatal diagnosis, a 0.999 probability of being a noncarrier.

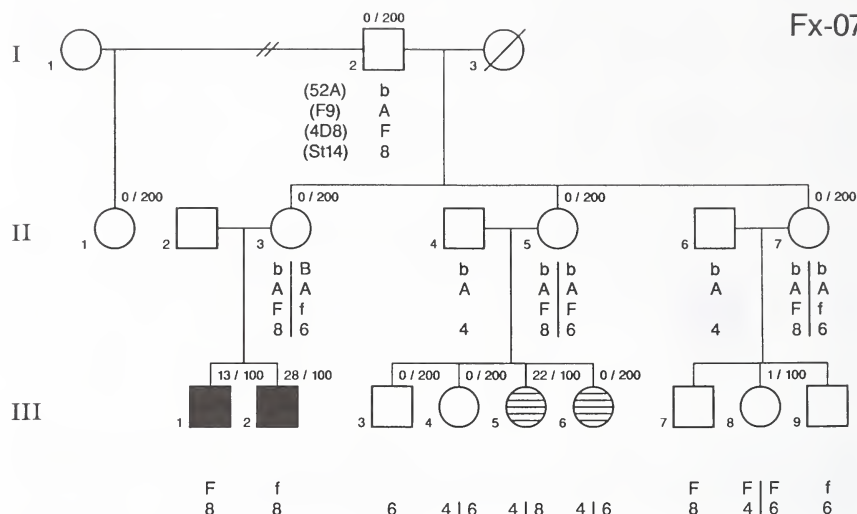


Fig. 2. Fragile X pedigree in which I-2 was shown to be a nonpenetrant male by DNA linkage analysis. II-1 was therefore counseled as an obligate carrier. Solid indicates mental retardation, hatched indicates learning disabilities.

Example 4 (Fig. 4)

Case FX-84 is similar to but more complicated than Case FX-39. Cytogenetic analysis on IV-1, III-2, III-6 and III-7 in combination with physical and cognitive evaluations, confirmed the fragile X gene's presence in this family. After the family was first seen in 1987, I-3 presented to our clinic for further evaluation. Testing on two occasions demonstrated 2/200 and 1/150 cells fragile X-positive. This, in combination with mental retardation, strongly suggested fragile X syndrome. As a consequence, I-2 was counseled as a possible carrier. Before evaluating I-2's extended family, DNA analysis was performed as confirmation and to provide carrier probabilities to III-3, III-4 and III-5 (all of whom tested fragile X-negative). Unexpectedly, I-1 was found to be a nonpenetrant male with a probability of 0.99. This greatly reduced the risk for II-3, who was previously counseled as having a 19% risk of being a nonpenetrant male, and afforded III-3, III-4 and III-5 probabilities of 0.92 or greater of being noncarriers. We are now in the process of evaluating I-1's extended family. Further genetic evaluation on I-3 is also indicated to determine other possible causes of her mental retardation. Low expression of the fragile X site, in this case, may well represent a false-positive.

Example 5 (Fig. 5)

Case FX-63 is a family who had concerns about their healthy daughter III-3. Cognitive testing, physical examination and cytogenetic testing were

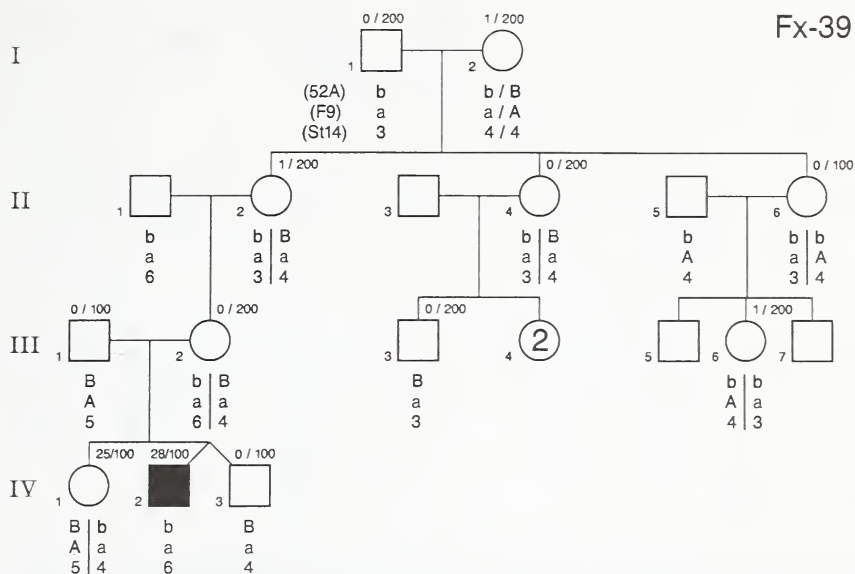


Fig. 3. Fragile X pedigree in which II-1 is likely a nonpenetrant male and III-6 is shown to be a noncarrier by DNA linkage analysis. Solid indicates mental retardation.

negative for any signs of fragile X syndrome. In taking the extended family history from II-2, there was a question of a maternal first cousin with mental impairment. For family reasons, it was unlikely that we would be able to test this individual.

DNA linkage analysis was performed on the relatives shown in Figure 5. Individual III-3, when the mutation rate was considered 2.4×10^{-4} , is likely to be normal with a probability of 0.73.

Her probability of being normal was 0.24 when the mutation rate was entered as zero. More recently, fragile X testing was finally arranged for II-4. He was, in fact, fragile X-positive. As a consequence, III-3's risk of being a carrier is approximately 73%. Although there is still a possibility that she is a noncarrier, this information has provided the family, and more specifically, III-3, with valuable information pertinent to family planning.

Example 6 (Fig. 6)

It is important to be aware of some of the problems inherent in DNA linkage analysis of fragile X syndrome. As previously discussed, recombination frequency appears high in some fragile X families. FX-18 considered DNA linkage analysis to determine carrier status in III-7 and III-8. Previous risks were calculated at 40% of being a carrier (see Example 1). Although

Fx-84

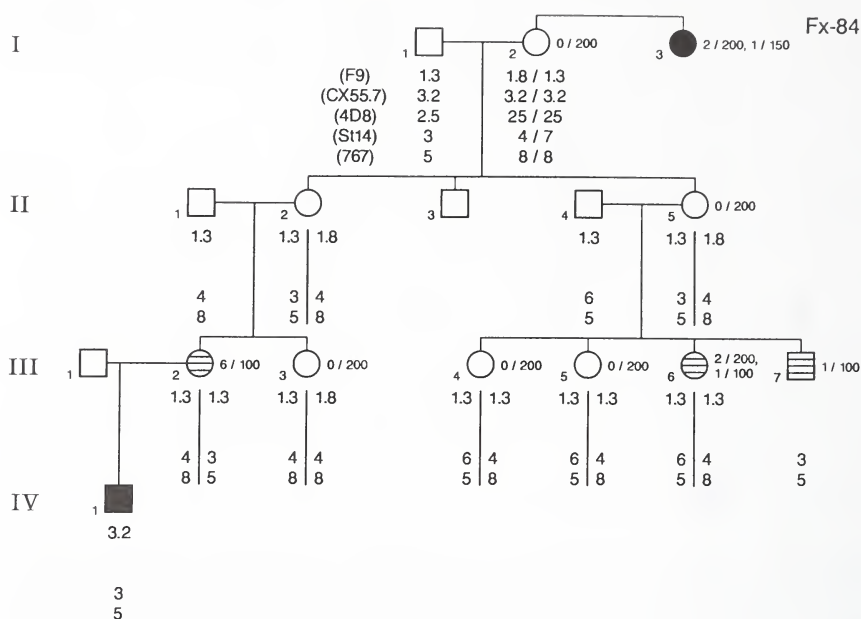


Fig. 4. Fragile X pedigree in which I-1 is shown to be a nonpenetrant male; III-3, III-4 and III-5 are likely to be noncarriers by DNA linkage analysis. Solid indicates mental retardation, hatched indicates learning disabilities.

DNA analysis gave III-7 a 0.98 probability of being a noncarrier, III-8 demonstrated a recombination between the flanking markers CX55.7 and St14, we elected not to calculate her carrier risk. Approximately a 70% risk of being a carrier had been given to II-6, yet she opted not to have prenatal diagnosis during any future pregnancies. Only recently, II-6 returned to our clinic for evaluation of her 16-month-old son who is speech delayed. Subsequent cytogenetic studies on this son and her 5-year-old daughter were fragile X positive and clinical evaluation indicated both are affected by fragile X syndrome.

DISCUSSION

Overall, there have been many advances in the diagnosis and treatment of fragile X syndrome. Nevertheless, genetic counseling can appear overwhelming if we take into account variable expressivity, variable penetrance and some of the other more perplexing aspects of this unique syndrome. Fortunately, Navajas et al (1987) and Weaver and Sherman (1987) have helped with the task of calculating recurrence risks. Information from careful clinical assess-

Fx-63

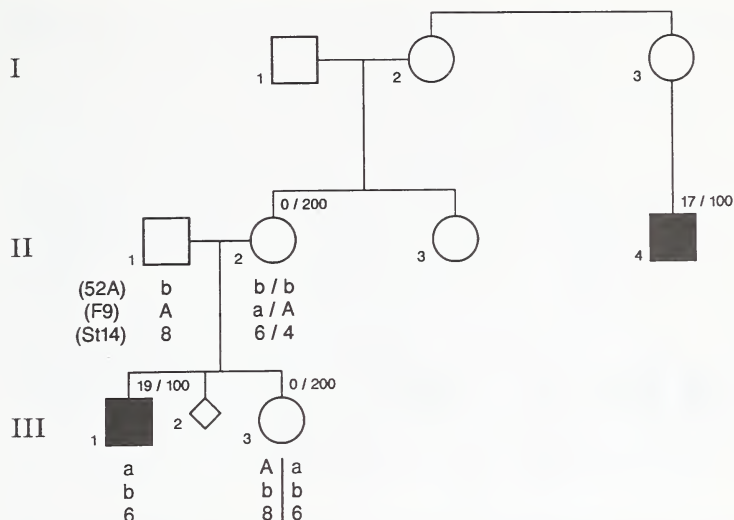


Fig. 5. Fragile X pedigree demonstrating importance of fragile X diagnosis in II-4 in interpreting DNA linkage analysis results on III-3. Solid indicates mental retardation.

ments and cytogenetic studies may serve as additional tools to provide accurate carrier probabilities. DNA analysis certainly promises to play a key role as we move closer to the fragile X locus. However, while it is comforting to know that these techniques are available and useful, we must not overlook their limitations.

Cytogenetic testing alone is useful in diagnosing affected individuals, but will detect only 26% of mentally normal heterozygous females and less than 1% of nonpenetrant males (Sherman et al, 1985). Low expressing fragile X positive individuals, as presented in examples 3 and 4, can further confuse the issue. Example 5 emphasizes the importance of taking a thorough pedigree and evaluating all at-risk individuals. This example illustrates that pedigree data (even from relatives not participating in DNA family studies) can greatly influence recurrence risks. As shown in examples 1 and 2, as well as by others (Brown et al, 1987a; Forster-Gibson et al, 1986; Mulley, et al 1987; Thibodeau et al, 1988), the combination of chromosome analysis, clinical evaluation, cognitive assessment and DNA linkage analysis helps one to avoid counseling errors and to maximize the accuracy of carrier probabilities and prenatal diagnosis.

Even under optimal circumstances, where all testing and evaluations are performed preconceptionally, inconclusive or problematic results may present in the fetus that require interpretation. Variable expression in males and

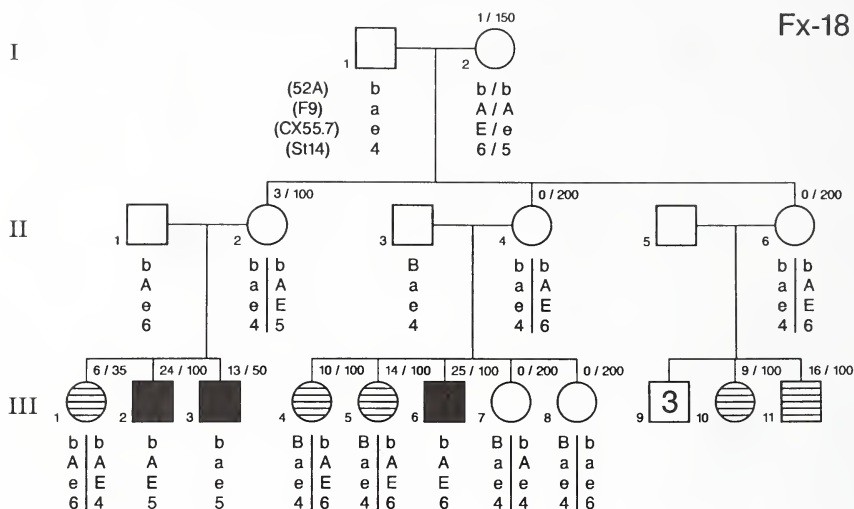


Fig. 6. Fragile X pedigree showing likely recombination in II-2 and recombination in III-1, III-3, III-7 and III-8. Solid indicates mental retardation, hatched indicates learning disabilities.

females makes the predictive value of prenatal cytogenetic results questionable. It is generally agreed that a cytogenetically positive male fetus ($\geq 4\%$) will be affected by the fragile X syndrome. Voelckel et al (1988), however, have reported isolated cases in which there is a dissociation between mental impairment and fragile X expression. High frequency of fragile X expression in healthy, normal functioning males has also been reported by Brown et al (1986), Veenema et al (1987), and Turner and Partington (1988). It is unclear from these reports whether these are truly nonpenetrant males, or examples of higher functioning fragile X males. A third possibility is that this may represent expression of a common fragile site. More recently, Voelckel et al (1989) reported an entire family in which numerous relatives demonstrated a high frequency of fragile X expression but none are mentally impaired. These authors suggest that this may be the first reported case of recombination between the fragile X locus, Xq27.3, and the fragile X gene(s). These reports are worrisome, especially with regard to prenatal diagnosis.

A low expressing male fetus ($<4\%$) can also be problematic since it may represent a false-positive. The male fetus may be affected, may be a nonpenetrant male or may be a learning disabled, normal IQ, fragile X male. Similarly, a cytogenetically negative but DNA-positive male fetus might represent a nonpenetrant male (Shapiro et al, 1988).

Similar uncertainties exist regarding the female fetus. To date, most couples chose to continue a pregnancy involving a female fetus. A cytogeneti-

cally negative or low expressing female fetus would be expected to carry a very low risk for mental impairment. Cronister et al (1991b), however, suggest that as many as 56% of cytogenetically positive females ($\geq 2\%$) are mentally impaired (IQ < 85). Certainly, this warrants further investigation and may have serious implications for prenatal genetic counseling.

These issues, in combination with the possibility of recombination, lack of informative probes and even nonpaternity, are dilemmas that potentially face genetic counselors and their patients. Advancements in prenatal diagnostic techniques, improvements in cytogenetic and DNA technology, and a better understanding of fragile X inheritance will help to rectify this situation. In the meantime, preconceptional counseling, although not always an option, is helpful to prepare families for uncertainties. Similarly, cytogenetic testing, DNA linkage analysis and other evaluations are strongly encouraged prior to undergoing a pregnancy and must be performed in an experienced center. Only in this way can the utility of testing and its limitations be determined and thoroughly discussed.

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DNA Diagnosis of Cystic Fibrosis: Utilization of Genetic Counseling

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INTRODUCTION

The identification of a marker linked to the cystic fibrosis (CF) locus on the long arm of chromosome 7 in 1985 stimulated a widespread interest in clinical DNA testing. DNA markers that were in linkage disequilibrium were identified in 1987. Yet this RFLP gene tracking method is indirect, not detecting the pathologic mutation itself but taking advantage of nearby innocent DNA variation to track the pathologic allele. As such it requires DNA from at least one affected family member. Thus, this DNA marker linkage analysis may not be possible in families in which the only person having CF has died. Moreover, linkage analysis requires family cooperation in order to obtain blood samples for DNA from both parents and often other relatives.

In general, when the risk is 10% or greater that a disorder will occur again in a subsequent pregnancy, couples make substantial changes in their childbearing plans and, when available, may elect to use prenatal diagnosis and to consider the selective termination of pregnancies in which the fetus is found to be affected. There were strong indications in 1985 that this would hold true in CF, a disorder that affects 1/2,500 newborns in the caucasian population and in which half of the patients die by age 26 years despite all available modern treatments and often after many years of severe pulmonary symptoms. We sought to identify some of the psychosocial factors that influence family decision-making with regard to the actual application of the new RFLP technology to the prenatal diagnosis of cystic fibrosis.

In 1984, before DNA prenatal diagnosis of CF was possible, Michael Kaback and associates surveyed 204 California families having one or more children with CF. The families were questioned about their reproductive attitudes and childbearing plans, and how these might change if an accurate prenatal test were to be developed. Seventy-eight percent of respondents believed that prenatal diagnosis of cystic fibrosis would provide an important

option for families at risk. Thirty-two percent of parents stated that their own personal reproductive plans would have changed had a prenatal test been available earlier.

The purpose of our study was to identify factors that influenced utilization of DNA testing for CF by families at risk. The methods for our study were as follows. We designed and field tested a questionnaire which asked families about demographic information, health status and life expectations with regard to the affected child, out-of-pocket expenses and insurance coverage, personal reproductive plans, knowledge of the new technology, and attitudes toward abortion under various circumstances. A separate questionnaire surveyed the knowledge and attitudes of *adults* with CF. Data were analyzed using SPSS-X, a statistical package frequently used for analysis of social science data.

METHODS

Eleven regional CF clinics in all six New England states distributed anonymous, voluntary questionnaires. In seven centers, distribution took place at the time of a scheduled visit. The remaining four centers mailed questionnaires to families. We are in the process of supplementing data from the questionnaires with information gained from personal interviews with a sub-sample of families.

RESULTS AND DISCUSSION

To date, 305 questionnaires have been returned and analyzed; 217 of these are from parents of affected children and 88 from adults with CF. Major reasons that families did *not* utilize CF DNA testing were as follows: no additional children were intended; the families were optimistic regarding the present and future health of their affected child; a majority reported personal opposition to abortion for CF; and parents demonstrated limited knowledge of DNA technology.

With regard to the reproductive status of parents of affected children, the majority did not intend to have more children; indeed, 52% of respondents had been surgically sterilized; 17% were either over 45 years of age, widowed or divorced; and only 33% were fertile couples—the biologic parents of the affected child—residing in the same home.

Of the surgically sterilized sub-group, 61% reported that having a child with CF affected their decision to become sterilized. Seventeen percent of the sterilized respondents indicated that they would definitely attempt to reverse sterilization if they could be certain that a future child would not be affected, and an additional 20% were unsure.

Among the 71 fertile parents at risk for having a child with CF, 51% were planning more children, while 49% reported that they did not plan to have more children. Overall, a substantial number (58%) stated that they would alter their reproductive plans if they could be certain that their future offspring would not have CF.

In general, parents were extremely optimistic about the present and future health of their affected child. Of particular interest were parent responses to expected longevity and number of hospitalizations. Over half (57%) of all parents expected their child to live for 40 or more years. Most (59%) did not anticipate hospitalization in the next two years. Only 12% expected more than two hospitalizations.

When considering quality of life issues, both parents of affected children and adults with CF were similarly optimistic about the future. More than 65% of parents predicted that those with CF would live independently and be fully employed. Almost half anticipated marriage and parenting for the affected individual.

Whereas 56% of parents would themselves abort for severe mental retardation, only 20% would abort for CF. While the difference was not as great when comparing CF to moderate mental retardation, the presence of mental retardation seemed to be a stronger factor than CF in influencing respondents' decision to abort. By way of comparison, the highest percentage would choose abortion if the mother's life were in danger (79%) or in cases of pregnancy resulting from rape (72%) or incest (73%).

Respondents' knowledge with respect to DNA testing and its applications was highly variable. Though a significant number of both parents (91%) and affected adults (83%) accurately described carrier testing, only 63% of parents and 57% of adults knew that prenatal diagnosis was possible for relatives of affected patients. When asked if they had heard of various terms, most responded affirmatively to the more commonly used terms, such as carrier testing (86%), amniocentesis (81%) and DNA marker testing (68%). There was much less recognition of the more technical terms, such as polymorphism (13%) and RFLP (3%). Surprisingly, almost as many respondents said that they had heard of our control nonsense term, "synapse analysis" (19%), as had heard of chorionic villus sampling (25%).

Actual utilization of DNA testing for CF was low. Only 7–8% had undergone DNA testing. Of the 217 responding parents, 13% (27) had undergone DNA testing. Not surprisingly, 17 of these 27 parent users came from the fertile, at-risk group.

Despite the small number of actual users, we analyzed our data looking for characteristics associated with intention to use prenatal diagnosis within the parents' group as a whole. As expected, plans to have additional children were significantly associated with intention to use prenatal diagnosis. Similarly

associated was a good working knowledge of the current status of testing. These parents were more likely to know that prenatal diagnosis is available for CF and had heard of CVS and DNA marker testing. Families were more likely to consider prenatal testing if insurance covered the costs. Of the 22 who would use prenatal diagnosis, 12 would prepare for the birth of a child with CF, 7 would prevent the birth of a CF child, and 10 would get information to make a decision about abortion.

Finally, those intending to use prenatal diagnosis were more likely to have received prior genetic counseling from a genetic counselor, geneticist or CF physician; and were more likely to have specifically discussed prenatal diagnosis of CF. Of the 217 parents, 36% reported having genetic counseling. Twenty-nine percent reported that they were counseled by a medical geneticist or genetic counselor. Respondents viewed geneticists and genetic counselors as more likely to be neutral and supportive of individual decisions than their CF physicians.

Factors not associated with intention to use prenatal diagnosis were: religion, education, child's health, beliefs about life expectancy, occupation and family cooperation in giving blood samples for DNA testing. The sub-group of 71 fertile, at-risk parents (58 families) perhaps constitute the respondents most likely to be affected by the availability of prenatal diagnosis.

Of the 71, twenty-two reported that they either had used or intended to use prenatal testing. This sub-group knew that prenatal diagnosis was available for CF, had insurance which covered testing, and were more likely to consider abortion of an affected fetus, particularly if diagnosed in the first trimester. In this subgroup, religion/church attendance and education were not associated with intentions to use the technology.

At this point in our data collection and analysis, we believe the following factors are affecting families' decisions to use DNA testing:

- A majority of CF families do not intend to have additional children.
- Parents are generally optimistic about the future health status and quality of life of their affected children.
- Specific knowledge of CF families about DNA testing and prenatal diagnosis is variable; those having received genetic counseling are the best informed about these issues.
- Parents have a predominantly negative attitude toward abortion of affected fetuses.
- And, finally, a significant number of parents indicate that they would alter their reproductive plans if they could be certain that their offspring would not have CF.

DNA Testing: Carrier, Carrier—Who Is the Carrier?

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INTRODUCTION

Hemophilia A is an X-linked inherited disorder affecting approximately 1/10,000 white males. It is estimated that one-third of all cases have no previous family history of the disease, and may represent new mutations [1].

One of several hemorrhagic coagulation disorders, hemophilia A results from a defect or deficiency of the factor VIII clotting protein. A low level of coagulation activity is generally present in affected males. The effects of the disorder range from mild to severe and are dependent upon the level of factor VIII coagulant activity in the plasma. Diagnosis of carrier females, based on factor VIII activity, has not been shown to be reliable due to wide variations in activity [2].

In the past, prenatal diagnosis of hemophilia A was limited to the combined use of amniocentesis, fetoscopy, and factor VIII testing. DNA analysis, however, provides the possibility of directly testing for the presence of the mutation [3].

CASE HISTORY

SR and her presumed identical twin sister, SS, were referred to the Genetics Center by the local hemophilia clinic because of a family history of hemophilia A. SR's first child, a son (MR), was diagnosed with hemophilia A shortly after circumcision, when prolonged bleeding occurred. His factor VIII activity was <1%. There was no other family history of hemophilia A. SR and SS were interested in pursuing DNA analysis to determine carrier status. Blood samples were obtained from various family members as noted in the pedigree (Fig. 1).

RESULTS

Carrier status regarding hemophilia A for SR and SS could not be determined at this time based on DNA marker analysis. However, the results identified that MR inherited the X chromosome from his maternal grandfa-

PEDIGREE:

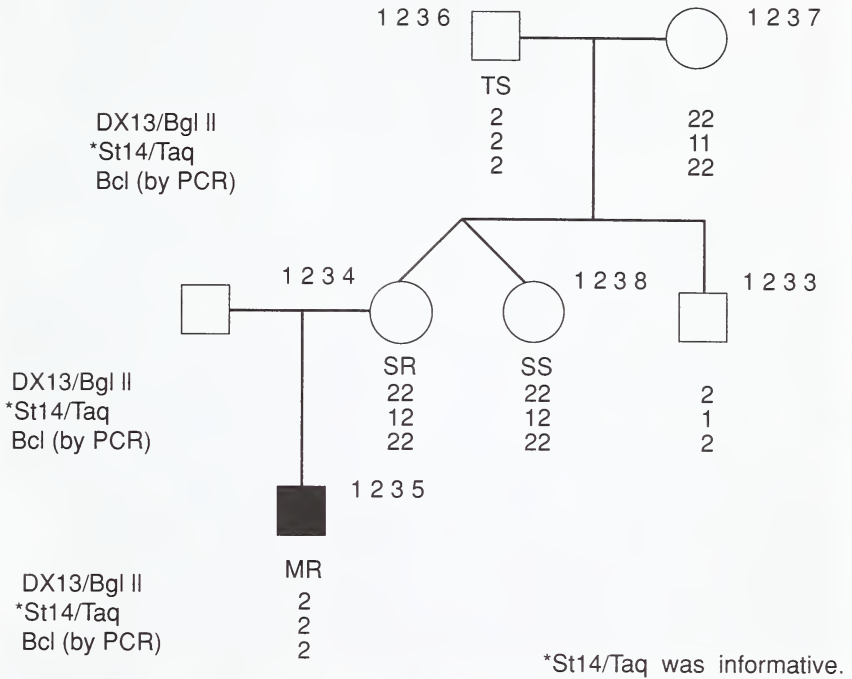


Fig. 1.

ther (TS), who is not affected. The autoradiograph and the pedigree present this information (Fig. 2).

DISCUSSION

Because there was no prior family history, it appears that there has been a *de novo* mutation. The dilemma is that it is not known where this mutation occurred—in the sperm that gave rise to SR or in the egg that gave rise to MR. A third consideration, not to be overlooked, is the possibility that SR may have gonadal mosaicism, as has been suggested recently in studies involving Duchenne muscular dystrophy [4]. Risks relating to this possibility cannot be assessed at the present time.

The challenge of genetic counseling is to provide information based on these results and the issues they pose to the family.

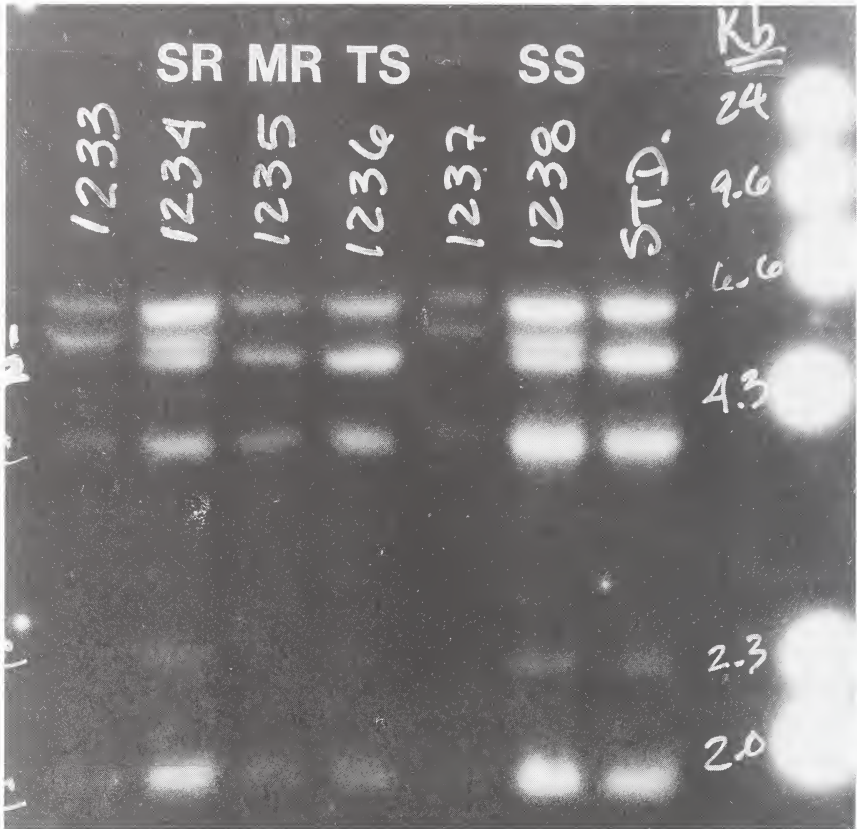


Fig. 2.

RECURRENCE RISKS

If MR's disease is the result of a new mutation in the egg that gave rise to him, the recurrence risk in a future pregnancy for SR is the mutation rate (approximately zero). If SR is a carrier and has another son, the risk of his being affected is 50%. Therefore, the risk in a future pregnancy for SR of having an affected son is the average of these two probabilities—25%.

A future pregnancy may clarify the carrier status of SR. An unaffected male who inherits the same grandpaternal X as MR would indicate that the mutation occurred in MR and that SR most likely is not a carrier. A male who is affected and has inherited the same grandpaternal X as MR, would indicate that the mutation occurred in SR and that she most likely is a carrier.

Family planning options. 1) pursue vs not pursue pregnancy; 2) adoption.

Prenatal test options. If SR would pursue another pregnancy, various prenatal evaluations are available for her consideration:

- 1) Genetic amniocentesis or chorionic villus sampling to determine which grandparental X the fetus has inherited. Inheritance of the grandmaternal X would indicate that the fetus was at a low risk for hemophilia A. However, if the grandpaternal X chromosome was inherited, the prediction of disease in a male, or carrier status in a female fetus, could not be made, based on the DNA analysis.
- 2) Fetoscopy or percutaneous fetal umbilical blood sampling for completion of factor VIII analysis. These procedures are not widely available and carry a greater risk for the pregnant woman and fetus.
- 3) Decline prenatal testing. After delivery, DNA analysis would be recommended to determine the inherited grandparental X. A male should have factor VIII testing completed prior to circumcision.

FAMILY CONSIDERATIONS REGARDING A FUTURE PREGNANCY

SR and her husband became aware that a number of issues were important for them to consider regarding their decision to have more children. These included:

- the meaning of the current DNA test results;
- their feelings regarding the recurrence of hemophilia A;
- the effect MR's disease and health status has had on the family;
- weighing the benefits/risks of having/not having prenatal testing;
- the importance of information gained from the various prenatal tests.

"IDENTICAL" TWIN SISTERS

SR and SS have been presumed to be identical twins their entire lives. This has not been determined at the DNA level. Counseling for SS is the same as for SR unless DNA evaluation proves that they are not identical. A pregnancy for SS may clarify carrier status for herself as well as SR.

CONCLUSION

For the genetic counselor, this case offered a unique opportunity to reflect on the impact that rapid advances in DNA analysis have on the counseling process. While we recognize the potential benefit of DNA analysis to evaluate carrier status and provide prenatal diagnosis, we must address the limitations inherent in specific tests.

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